ID1098 STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Crizotinib for treating ROS1-positive advanced non-small cell lung cancer [ID1098]

Confidential until published

This report supersedes all previous versions. This report was produced in response to the company's addendum of 23rd November 2017.

This report was commissioned by the NIHR HTA Programme as project number 16/119/03

Completed 19th December 2017

[redacted]

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Crizotinib for treating ROS1-positive advanced non-small cell lung cancer [ID1098]

Produced by: Liverpool Reviews and Implementation Group (LR*i*G)

Authors: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Angela Stainthorpe, Research Associate (Health Economics Modelling), LR*i*G, University of Liverpool

Marty Richardson, Research Fellow (Medical Statistician), LR*i*G, University of Liverpool

Rui Duarte, Health Technology Assessment Lead, LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Eleanor Kotas, Information Specialist, LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Pharmacy Practice Unit, Liverpool

John Green, Consultant in Medical Oncology, The Clatterbridge Centre NHS Foundation Trust, Liverpool

Correspondence to: Janette Greenhalgh, Liverpool Reviews and Implementation Group, University of Liverpool, 2nd Floor, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 14th November 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/119/03

Declared competing interests of authors: None

Acknowledgements: The authors would like to thank Dr Carles Escriu, Consultant Medical Oncologist, The Clatterbridge Centre NHS Foundation Trust, Liverpool and Dr Raffaele Califano, Consultant in Medical Oncology, The Christie NHS Foundation Trust, Manchester for their feedback on a final draft version of the report.

The authors thank Professor Peter Clark, Consultant Medical Oncologist, The Clatterbridge Centre NHS Foundation Trust, Liverpool and Dr Yvonne Summers, Consultant in Medical Oncology, The Christie NHS Foundation Trust, Manchester for their opinions on the generalisability of outcomes from people with ALK+ advanced NSCLC to people with ROS1+ advanced NSCLC.

Dr Escriu has received speaker fees from Pfizer Ltd. Dr Califano has received fees from Pfizer Ltd for consultancy, organising education, speaking and hospitality.

Rider on responsibility for the report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Greenhalgh J, Stainthorpe S, Richardson M, Duarte R, Boland A, Kotas E, McEntee J and Green J. Crizotinib for treating ROS1-positive advanced non-small cell lung cancer [ID1098]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2017.

Contributions of authors:

Greenhalgh J	Project lead, critique of the clinical evidence, drafted the clinical results section and supervised the final report
Stainthorpe A	Checking and validation of the economic model and critique
Richardson M	Critical appraisal of the statistical evidence
Duarte R	Critical appraisal of the clinical and economic evidence
Boland A	Critical appraisal of the clinical and economic evidence
Kotas E	Cross-check of the company submission search strategy
McEntee J	Critical appraisal of the company submission
Green J	Clinical advice and critical appraisal of the clinical evidence

All authors read and commented on draft versions of the ERG report.

Table of contents

List of tables

List of figures

LIST OF ABBREVIATIONS

AE	adverse event
ALK	anaplastic lymphoma kinase
AIC	Akaike Information Criterion
ASCO	American Society of Clinical Oncology
BIC	Bayesian Information Criterion
BSA	body surface area
CDF	Cancer Drugs Fund
CI	confidence interval
CRUK	Cancer Research UK
CS	company submission
CSR	clinical study report
DCR	disease control rate
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EGFR	epidermal growth factor receptor
EORTC	European Organisation for the Treatment of Cancer
EORTC QLQ-C30	European Organisation for the Treatment of Cancer quality of life questionnaire C30
EPAR	European Public Assessment Report
EQ-5D-3L	European quality of life-3 dimensions
ERG	Evidence Review Group
FAD	Final Appraisal Determination
FISH	fluorescence in situ hybridisation
H-H	cumulative hazard versus cumulative hazard
HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
IHC	immunohistochemistry
ITT	intention-to-treat
IV	intravenous
IVRS	interactive voice recognition system
K-M	Kaplan-Meier
KRAS	Kirsten rat sarcoma virus
LCH	log-cumulative hazard
LCHP	log cumulative hazard plots
LY	life year
LYG	life years gained
MIMS	Monthly Index of Medical Specialities
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PD	progressive disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PH	proportional hazards
PS	performance status
PSA	probabilistic sensitivity analysis

PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality adjusted life year
RCT	randomised controlled trial
RECIST	response evauation criteria in solid tumours
RR	relative risk
RTK	receptor tyrosine kinases
SAP	statistical analysis plan
SmPC	summary of product characteristics
STA	single technology appraisal
WTP	willingness to pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical evidence and economic evidence have been submitted to NICE by Pfizer Limited in support of the use of crizotinib (Xalkori®) for ROS1-positive (ROS1+) advanced non-small cell lung cancer (NSCLC).

Crizotinib is licensed in Europe for the treatment of patients with ROS1+ advanced NSCLC. Crizotinib is also licensed in Europe for the treatment of adults with anaplastic lymphoma kinase-positive (ALK+) advanced NSCLC.

1.2 Critique of the decision problem in the company submission

Population

The population described in the final scope issued by NICE is people with ROS1+ advanced NSCLC. The population discussed in the company submission (CS) is the population recruited to the PROFILE 1001 study, which is identical to the population described in the final scope. However, data from this small, single-arm study are limited (n=53). The company has used data from a population of patients with ALK+ advanced NSCLC as proxy data for a population of patients with ROS1+ advanced NSCLC.

Treatment line is not specified in the final scope issued by NICE or in the European Medicines Agency (EMA) licence. The company expects that crizotinib will be used as a first- and subsequent-line treatment. However, the company anticipates that the number of patients treated at subsequent-line will reduce over time as patients with ROS1+ advanced NSCLC will be identified when they first present with NSCLC symptoms and treated with crizotinib in the first-line.

In the absence of randomised controlled trial (RCT) evidence for the efficacy of crizotinib in patients with ROS1+ advanced NSCLC, the company uses data from RCTs conducted in patients with ALK+ advanced NSCLC as a proxy for the outcomes of patients with ROS1+ advanced NSCLC. The company considers that ROS1+ and ALK+ advanced NSCLC are similar diseases and that patients with ROS1+ and ALK+ advanced NSCLC have similar characteristics. The ERG considers that the company has focussed on the population specified in the decision problem only if the outcomes from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC.

Intervention

Crizotinib is licensed in Europe for the treatment of patients with ROS1+ advanced NSCLC. Crizotinib is administered as hard capsules at a dosage of 250 mg twice daily.

Comparators

The final scope issued by NICE sets out different comparators for (i) people with ROS1+ advanced NSCLC who have not had previous treatment and (ii) people with ROS1+ advanced NSCLC who have received previous chemotherapy treatment.

Direct evidence. No direct evidence is available for crizotinib versus any of the comparators specified in the final scope issued by NICE.

Proxy evidence. Proxy evidence is presented in the CS for the comparison of the effectiveness of crizotinib versus pemetrexed+platinum in patients with previously untreated ALK+ advanced NSCLC. Evidence is also presented in the CS for the comparison of the effectiveness of crizotinib versus chemotherapy (pemetrexed or docetaxel monotherapy) in patients with ALK+ advanced NSCLC who have had previous treatment with chemotherapy.

No evidence. No evidence is presented in the CS for the comparisons of crizotinib for untreated disease with: i) a third generation chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) with a platinum drug (carboplatin or cisplatin), with (for people with non-squamous NSCLC only) or without pemetrexed; ii) single agent chemotherapy with a third generation drug for people who cannot tolerate platinum-based therapy; iii) pemetrexed+platinum (for people with adenocarcinoma or large cell only) with pemetrexed maintenance treatment.

No evidence is presented in the CS for the comparisons of crizotinib after previous chemotherapy with: i) docetaxel+nintedanib; ii) best supportive care (BSC). Treatment with docetaxel+nintedanib in the subsequent care setting is the NHS standard of care for patients with tumours of adenocarcinoma histology.

Outcomes

For the patient population specified in the final scope issued by NICE, i.e., patients with ROS1+ advanced NSCLC, data for progression-free survival (PFS), objective response rate (ORR), overall survival (OS) and adverse events (AEs) are derived from the PROFILE 1001 study. However, median OS has not been reached and the company does not intend to carry out further updates of OS until [redacted] Health-related quality of life (HRQoL) data were not collected.

Comparative clinical effectiveness analyses presented in the CS are based on data evaluating the use of crizotinib in ALK+ advanced NSCLC patients as a proxy for data from ROS1+ advanced NSCLC patients. Outcome data for patients with untreated ALK+ advanced NSCLC are available from the PROFILE 1014 trial. Data are presented in the CS for the outcomes of PFS, objective response rate (ORR), AEs and HRQoL. Outcome data for patients with previously treated ALK+ advanced NSCLC are available from the PROFILE 1007 trial. Data are presented in the CS for the outcomes of PFS, ORR, AEs and HRQoL. Data for OS are available from both the PROFILE 1014 and PROFILE 1007 trials; however, high levels of crossover occurred in both trials. This means that the true OS associated with crizotinib in patients with untreated ALK+ advanced NSCLC and patients with previously treated ALK+ advanced NSCLC is unknown.

Other considerations

In the summary of product characteristics for crizotinib, it is stipulated that treatment should only be initiated after the patient's ROS1 status has been positively confirmed by a clinical laboratory test using a validated test method. There is currently no routinely funded testing of patients for ROS1 in the NHS. The company points out that if the sequential testing strategy, rather than upfront testing, for the identification of ROS1+ advanced NSCLC is adopted in the NHS, there is the potential for a delay in the diagnosis and treatment of patients.

The existing Patient Access Scheme agreement in place for crizotinib for the treatment of patients with ALK+ advanced NSCLC will be extended to include the ROS1+ patient population.

The company has put forward a case for crizotinib to be considered against the NICE End of Life criteria.

1.3 Summary of clinical effectiveness evidence submitted by the company

Direct evidence

The company presents evidence for the clinical effectiveness of crizotinib from the PROFILE 1001 study. The PROFILE 1001 study was a single-arm study in which patients with ROS1+ advanced NSCLC were treated with 250 mg of crizotinib twice daily until disease progression. Of the 53 recruited patients, 7 patients had untreated disease and 46 patients had received at least one prior chemotherapy. Most of the 53 patients achieved either a partial or complete response with crizotinib (69.8%), and median PFS was 19.3 months (95% confidence interval [CI]: 14.8 to not reported [NR]). OS data were immature, with only 30% of patients having died at the latest data cut-off date. The most frequently occurring AEs of any grade were vision disorders; these were Grade 1 or Grade 2. The Grade 3 AEs reported included hypophosphataemia and neutropenia. No Grade 4 AEs were recorded. No HRQoL data were collected during the PROFILE 1001 study.

Proxy evidence

The company presents data from the PROFILE 1014 trial in which patients with previously untreated ALK+ advanced NSCLC were randomised to receive treatment with crizotinib 250 mg twice daily (n=172) or pemetrexed+platinum chemotherapy (n=171). Most of the patients treated with crizotinib achieved a partial or complete response (74%) compared with 45% of patients treated with pemetrexed+platinum. Median PFS for patients treated with crizotinib was 10.9 months compared with 7 months for patients treated with pemetrexed+platinum (hazard ratio [HR]=0.45, 95% CI: 0.35 to 0.60; p<0.001). Median OS was not reached for patients treated with crizotinib and was 47.5 months for patients treated with pemetrexed+platinum. Patient crossover from pemetrexed+platinum to crizotinib was 84.2%.

The company presents data from the PROFILE 1007 trial in which patients with previously treated ALK+ advanced NSCLC were randomised to receive treatment with 250 mg of crizotinib twice daily (n=173) or intravenous chemotherapy that was either pemetrexed or docetaxel monotherapy (n=174). Most of the patients treated with crizotinib achieved a partial or complete response (65.3%) compared with 19.5% of patients treated with chemotherapy. Median PFS for patients treated with crizotinib was 7.7 months compared with 3 months for patients treated with chemotherapy (HR=0.49, 95% CI: 0.37 to 0.64; p<0.0001). Median OS was similar in both arms; 21.7 months for patients treated with crizotinib and 21.9 months for patients treated with chemotherapy. Patient crossover from chemotherapy to crizotinib was 88.5%.

The HRQoL results (EQ-5D) appeared to show a benefit of treatment with crizotinib compared with chemotherapy. The type of and incidence of AEs from a pooled analysis of data from the PROFILE 1014 and 1007 trials and two single-arm studies were consistent with the AEs experienced by patients in the PROFILE 1001 study.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers that the company has addressed the decision problem only if the outcome data from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC.

The ERG is satisfied with the company's search strategy and stated inclusion and exclusion criteria. The ERG is confident that searching was carried out to an acceptable standard and is not aware of any additional studies that should have been included in the company's systematic review.

Direct evidence

The ERG considers that the PROFILE 1001 study is generally of good quality with independent assessment of radiological outcomes, and that the patients recruited to the study are representative of patients who are likely to be treated in the NHS. However, the PROFILE 1001 study is small and only 7 of the 53 patients had untreated disease. Of the patients with previously treated disease, only 37% had received the NHS standard of care in the first-line setting, i.e., pemetrexed+platinum chemotherapy. The OS data from the study are immature and no HRQoL data were collected.

Proxy evidence

The ERG considers the PROFILE 1014 trial to be a good quality trial. Clinical advice to the ERG is that patients recruited to the trial are generally representative of patients with ALK+ advanced NSCLC who are treated in clinical practice in the NHS. However, the ERG notes that in the company's economic model, adjustments were made to the PROFILE 1014 trial population based on the characteristics of patients included in a retrospective cohort study conducted in the US and Canada. A previous appraisal committee considered the adjustments to be conservative.

The ERG considers the PROFILE 1007 trial to be of good quality and that patients recruited to the trial are generally representative of patients with ALK+ advanced NSCLC who are treated in clinical practice in the UK.

The ERG considers that the proportional hazards (PH) assumption was not valid for PFS for either the PROFILE 1014 or PROFILE 1007 trials, and that hazard ratios (HRs) for PFS data from both trials should be interpreted with caution.

The ERG notes that there was a substantial amount of patient crossover from the chemotherapy arm to the crizotinib arm and vice versa in both the PROFILE 1014 and PROFILE 1007 trials. The company presents Rank Preserving Structural Failure Time Model (RPSFTM)-adjusted OS HRs to account for patient crossover in the PROFILE 1014 and PROFILE 1007 trials. The ERG considers that the RPSFTM-adjusted HRs for OS are unlikely to be valid and should be interpreted with caution.

When comparing the ORR results of the PROFILE 1001 study, the PROFILE 1014 trial and the PROFILE 1007 trial, the ERG considers that the ORR results are similar at 69.8%, 74.4% and 65.3% respectively. The results from both the PROFILE 1014 and PROFILE 1007 trials demonstrated a statistically significantly greater ORR for crizotinib patients than for chemotherapy patients.

In comparing the PFS results of the PROFILE 1001 study, the PROFILE 1014 trial and the PROFILE 1007 trial, the ERG considers that median PFS is not similar at 19.3 months (95% CI: 14.8 to not reported), 10.9 months (95% CI: 8.3 to 13.9), 7.7 months (95% CI: 6.0 to 8.8) respectively. The differences in PFS cause the ERG to question whether the ROS1+ and ALK+ advanced NSCLC patient populations are truly similar.

The ERG notes that there are no mature OS data available for patients with ROS1+ advanced NSCLC. The ERG also notes that the OS data from patients with ALK+ advanced NSCLC presented in the CS from the PROFILE 1014 are immature. Overall survival data from the PROFILE 1014 and 1007 trials are both confounded by patient crossover. This means that there are no conclusive OS data from either the population specified in the decision problem (i.e. people with ROS1+ advanced NSCLC) or from the ALK+ advanced NSCLC population used in the CS to mitigate the uncertainty around the limited data available for the population specified in NICE's decision problem.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo cost effectiveness model structure in Microsoft Excel. The same model structure is used for the analysis of first- and subsequent-line treatment with crizotinib, but consider different comparator, cost, efficacy and benefit inputs applied to each population. The model comprises three progressively worse health states: progression-free disease, progressed disease and death. The company uses a 30-day cycle length and has

implemented a half-cycle correction. The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services (PSS) and the model time horizon is 20 years. The company states that both costs and benefits are discounted at a rate of 3.5% per annum.

The population reflected in the model is adults with ROS1+ advanced NSCLC. This is split into two populations to encompass first- and subsequent-line treatment with crizotinib. The comparator in the first-line setting is pemetrexed+platinum. The comparator in the subsequent-line setting is docetaxel. Due to the limited availability of time-to-event data for patients with ROS1+ advanced NSCLC, the company has used data from the ALK+ advanced NSCLC population as a proxy for data from ROS1+ patients in the base case analysis.

For the first-line population, extrapolations of PFS and time to treatment discontinuation (TTD) data for patients with ALK+ advanced NSCLC were taken from TA406 (based on the results of the PROFILE 1014 trial). The company has updated its modelling of OS since TA406 and has provided a new analysis based on an updated data cut (9 March 2017) from the PROFILE 1014 trial. Estimates of OS in the first-line model have been adjusted for crossover using the RPSFT method. The company has adjusted the baseline characteristics for all estimates of OS, PFS and TTD from the PROFILE 1014 trial to match the characteristics of patients who participated in a 'real-world' trial based in the UK.

For the subsequent-line population, extrapolations of OS, PFS and TTD data for patients with ALK+ advanced NSCLC were taken from TA422 (based on the results of the PROFILE 1007 trial). OS for treatment with crizotinib in the subsequent-line setting was estimated by applying the PFS HR from the PROFILE 1007 trial to the RPSFTM-adjusted estimates of OS for treatment with docetaxel from the same trial. Survival estimates have not been adjusted for patient baseline characteristics in the subsequent-line model.

The company has provided a scenario analysis using clinical effectiveness data for treatment with crizotinib in patients with ROS1+ advanced NSCLC from the PROFILE 1001 study. Estimates of clinical effectiveness for comparator treatments in the first- and subsequent-line settings have been calculated using HRs from the PROFILE 1014 and PROFILE 1007 trials respectively.

EQ-5D data collected in the PROFILE 1014 and PROFILE 1007 trials were used to estimate PFS utility values in the first- and subsequent-line models for both the base case analysis and the PROFILE 1001 scenario analyses. The utility value for patients treated with a second-line treatment in the first-line model was assumed to be the same as the PFS utility for docetaxel

in the subsequent-line model. A published utility value was used for patients in the first-line model who had completed post-progression treatment and moved onto BSC. The same BSC utility value was used for patients who had progressed after treatment in the subsequent-line model.

The company derived resource use and unit costs from a number of sources, including data from: PROFILE 1007 and PROFILE 1014 trials, national databases, previous technology appraisals of crizotinib in first- and subsequent-line ALK+ advanced NSCLC and clinical advice. The company used the PAS price for crizotinib in all of the cost effectiveness analyses presented in the CS.

In the first-line base case analysis, treatment with crizotinib generates incremental life years gained (LYG) (+2.39 years) and more benefits (+1.28 quality adjusted life years [QALYs]) than treatment with pemetrexed+platinum at an increased cost of [redacted]. The company base case incremental cost-effectiveness ratio (ICER) for the comparison of first-line treatment with crizotinib versus pemetrexed+platinum is [redacted] per QALY gained.

In the subsequent-line base case analysis, treatment with crizotinib generates incremental LYG (+1.36 years) and more benefits (+0.93 QALYs) than treatment with docetaxel at an increased cost of [redacted]. The company base case ICER for the comparison of subsequent-line treatment with crizotinib versus docetaxel is [redacted] per QALY gained.

In the first-line PROFILE 1001 scenario analysis, treatment with crizotinib generates incremental LYG (+3.60 years) and more benefits (+1.95 QALYs) than treatment with pemetrexed+platinum at an increased cost of [redacted]. The company base case ICER for the comparison of first-line treatment with crizotinib versus pemetrexed+platinum is [redacted] per QALY gained.

In the subsequent-line PROFILE 1001 scenario analysis, treatment with crizotinib generates incremental LYG (+3.43 years) and more benefits (+1.95 QALYs) than treatment with docetaxel at an increased cost of [redacted]. The company base case ICER for the comparison of subsequent-line treatment with crizotinib versus docetaxel is [redacted] per QALY gained.

1.6 Summary of the ERG's critique of submitted cost effectiveness evidence

The company's models are generally well-structured. However, as both the first- and subsequent-line models are contained in the same Excel file, the document is somewhat unwieldy.

Fundamental issues with the economic analysis

The ERG's principal concern is that it has been unable to check and verify many of the inputs into the economic models submitted by the company. The ERG has been unable to verify whether the models appropriately address the decision problem set by NICE for two key reasons:

1. The CS relies heavily on the assumptions and modelling approaches used in three previous STAs (TA406, TA422 and TA296). The company has not provided sufficient justification in the CS for the application of these assumptions and approaches in the current appraisal, beyond the fact that they were previously accepted.

2. Even if the ERG was able to verify the assumptions made by the company, lack of model functionality would impede the ERG's ability to investigate the effects of specific key assumptions in the model.

The company base case analysis is founded on the assumption that the outcomes of treatment with crizotinib in an ALK+ advanced NSCLC population are an appropriate proxy for the outcomes of treatment with crizotinib in a ROS1+ advanced NSCLC population. First- and subsequent-line treatments with crizotinib in an ALK+ advanced NSCLC population have been previously appraised by NICE (TA406, TA422 and TA296); therefore, much of the data and modelling included in the company base case analysis has been discussed in previous STAs. The ERG has prioritised the critique of newly available data in this appraisal (updated OS from the PROFILE 1014 trial and data from the PROFILE 1001 study). However, this does not imply that the ERG is satisfied that inputs and approaches not covered in this critique are appropriate and correctly implemented in the model.

Modelling issues

The company's first-line base case model yields a substantial post-progression survival (PPS) benefit for treatment with crizotinib versus pemetrexed+platinum, which means that the extra survival gained beyond progression constitutes 74% of total OS gain for treatment with crizotinib. This suggests that the treatment effect is better after progression than before progression and, therefore, that the OS treatment effect is better than the PFS treatment effect. The ERG acknowledges that there may be some PPS benefit attributable to treatment with crizotinib, especially since many patients are treated beyond progression. However, the ERG considers it questionable to model an OS treatment effect that is substantially better than the PFS treatment effect without robust evidence to support that assumption. The company's subsequent-line base case model also includes a post-progression treatment effect that is greater than the PFS treatment effect, although the proportion of OS gain accrued post-progression is smaller in the subsequent-line model than in the company's first-line model. The ERG has explored alternative methods of modelling OS treatment effect in the first- and subsequent-line settings to investigate the impact on the ICERs per QALY gained of reducing PPS gain.

The company's PROFILE 1001 scenario analysis is based on data from a small, immature, single-arm trial. Any modelling of this data will likely be subject to substantial uncertainty and the ERG notes that this is acknowledged by the company. However, the company has interpreted the results of its PROFILE 1001 analysis as evidence of reduced uncertainty in the modelling of treatment with crizotinib in a ROS1+ advanced NSCLC population, since the ICERs resulting from its PROFILE 1001 scenario analysis are less than £50,000 per QALY gained. The ERG has explored alternative ways of modelling the time-to-event data from the PROFILE 1001 study to investigate the impact on the ICER per QALY gained of other plausible extrapolation methods and assumptions about treatment effect.

Progression-free utility values used in the company's first-line model are based on EQ-5D response data collected in the PROFILE 1014 trial. This dataset includes only six cycles of responses from patients receiving pemetrexed+platinum versus 50 cycles of responses from patients receiving treatment with crizotinib. The ERG is concerned that the PFS utility value used by the company for patients treated with pemetrexed+platinum in the first-line model may not be representative of the whole time that these patients spend in the progression-free state, as it is based on EQ-5D responses collected only whilst patients are on treatment. The ERG also notes a difference in baseline PFS utility values across the two arms in the PROFILE 1007 trial which has not been adjusted for in the subsequent-line model. The ERG has

explored scenarios using different PFS utility values in the first- and subsequent-line models to investigate the impact of uncertainty around HRQoL.

The ERG has also noted minor issues with the cost of treating AEs and the cost of testing for ROS1 mutations.

1.7 Summary of company's case for End of Life criteria being met

The company has put forward the case that crizotinib meets NICE's End of Life criteria. The company reports that there are limited data for OS for patients with ROS1+ advanced NSCLC and that data from patients with ALK+ advanced NSCLC have been used as supportive evidence.

Life expectancy

For patients treated with chemotherapy, the company states that estimates of median OS in patients with ALK+ advanced NSCLC range between 6 months and 22 months and that median OS in the PROFILE 1007 trial was 21.9 months.

Extension to life of at least 3 months

The company states that PFS for patients with ROS1+ advanced NSCLC in the PROFILE 1001 study was 19.3 months. The company considers 19.3 months to be the minimum value for OS in this patient population and observes that the Appraisal Committee for TA422 accepted, that in the case of targeted therapies, PFS could be considered a conservative indicator of OS. The company also states that in TA422 and in TA406, the Appraisal Committee accepted that patients treated with crizotinib would gain an extension to life of more than 3 months compared with standard of care.

The company's economic models predict an extension to life for patients with ROS1+ advanced NSCLC of 2.39 years compared to pemetrexed+platinum therapy and 1.36 years compared to docetaxel therapy.

1.8 ERG commentary on End of Life criteria

The ERG considers that the evidence for life expectancy and extension to life in patients with ROS1+ advanced NSCLC is uncertain, particularly given the lack of a comparator in the PROFILE 1001 study. The ERG notes the following points from previous appraisals of crizotinib for patients with ALK+ advanced NSCLC:

- The Appraisal Committee in TA406 considered that life expectancy in the ALK+ advanced NSCLC population in the first-line setting was likely to be less than 24 months and that the short life expectancy criterion was met. This consideration was

made taking into account the company's revised model that used an earlier data cut from the PROFILE 1014 trial than is used in this appraisal. This consideration was made based on estimates of OS with adjusted baseline characteristics.

- The Appraisal Committee in TA422 noted that there was some uncertainty around life expectancy in the ALK+ advanced NSCLC population in the subsequent-line setting, but considered that, on balance, it was likely to be less than 24 months and that the short life expectancy criterion was met.
- The Appraisal Committee in TA422 and TA406 considered that treatment with crizotinib in the first-line and subsequent-line setting would offer at least 3 months of additional survival benefit in the ALK+ advanced NSCLC population. The Appraisal Committee concluded that the extension to life criterion was met.
- The ERG notes that the NHS standard of care for treatment of patients with advanced NSCLC of adenocarcinoma histology has recently changed and is now docetaxel+nintedanib (which has not been included as a comparator in this appraisal).

1.9 ERG commentary on the robustness of evidence submitted by the company

The appraisal of crizotinib for ROS1+ advanced NSCLC includes two company models that cannot be fully quality assured for the reasons outlined in the previous section. This also means that the ERG cannot be confident that the results of any additional exploratory analyses are reliable. As a result, the critique and information provided in this ERG report is limited and the ERG is unable to provide ERG preferred base case ICERs per QALY gained.

1.9.1 Strengths

Clinical effectiveness evidence

- The PROFILE 1001 study was of good quality with independent assessment of radiological results
- In the absence of any comparative evidence from a RCT in the ROS1+ population, the company made use of the data available from the PROFILE 1014 and PROFILE 1007 trials

Cost effectiveness evidence

- The economic model was well constructed
- The company carried out a comprehensive range of deterministic sensitivity and scenario analyses

1.9.2 Weaknesses and areas of uncertainty

Clinical effectiveness evidence

- Clinical advice to the company is that ROS1+ and ALK+ advanced NSCLC are similar diseases and that patients in these populations have similar characteristics. However, the ERG is uncertain if there is sufficient evidence available to allow the outcomes of patients with ALK+ advanced NSCLC to represent the outcomes of patients with ROS1+ advanced NSCLC
- There is no RCT evidence available to support the use of crizotinib for treating ROS1+ advanced NSCLC for any line of treatment
- The clinical evidence supporting treatment with crizotinib in the ROS1+ advanced NSCLC population is derived from a small, single-arm study (PROFILE 1001)
- The OS data from the PROFILE 1001 study were immature (30% of events had occurred at the time of the 2014 data analysis)
- The company was unable to compare crizotinib in patients with ROS1+ advanced NSCLC with any of the comparators listed in the final scope issued by NICE due to a lack of relevant clinical effectiveness evidence
- In the absence of RCT evidence in a population of patients with ROS1+ advanced NSCLC, the company has used data from RCTs that recruited patients with ALK+ advanced NSCLC (PROFILE 1014 and 1007)
- The company was unable to compare crizotinib versus docetaxel+nintedanib in the subsequent-line setting due to lack of published data

- The OS data from the PROFILE 1014 trial are immature and are confounded by crossover; data from the PROFILE 1007 trial are confounded by crossover
- The proportional hazard assumption is not valid for PFS for PROFILE 1014 and 1007 trials
- There are no reliable OS data available for patients treated with ROS1+ advanced NSCLC or patients with ALK+ advanced NSCLC
- There are concerns about the generalisability of the adjusted results of the PROFILE 1014 trial. Clinical advice to the ERG is that patients in the PROFILE 1001 study and patients in the PROFILE 1014 and 1007 trials have similar baseline characteristics and broadly represent patients likely to be treated in the NHS

Cost effectiveness evidence

- The evidence underpinning the base case first- and subsequent-line models is from a proxy population (ALK+ advanced NSCLC) rather than the population of interest (ROS1+ advanced NSCLC). The impact of this assumption on cost effectiveness estimates is unknown, since the evidence for the ROS1+ advanced NSCLC population is severely limited
- The evidence used to estimate time-to-event data for treatment with docetaxel in the subsequent-line setting is based on the pooled results of treatment with pemetrexed and docetaxel. The impact of this assumption on cost effectiveness estimates is unknown, although the assumption is expected to be conservative
- The OS evidence for the proxy ALK+ advanced NSCLC population is compromised in both first- and subsequent-line models, which leads to substantial uncertainty in the modelling of OS in the base case analyses
- Estimates of PPS gain in the first- and subsequent-line base cases are substantially greater than estimates of PFS gain. This means that OS treatment effect is modelled to be greater than the PFS treatment effect, which the ERG does not consider to be supported by the evidence available
- Estimates of OS, PFS and TTD in the PROFILE 1001 scenario analysis are based on parametric models with low levels of face validity and clinical plausibility
- Utility values for treatment with pemetrexed+platinum in the progression-free state in the first-line setting are based on only six cycles of EQ-5D data, which may bias the mean result
- There are differences in the baseline EQ-5D data collected during the PROFILE 1007 trial across the two trial arms. These data have not been adjusted for and may bias the mean utility values used for PFS in the subsequent-line model
- Testing for ROS1 rearrangements in the subsequent-line setting is assumed to be carried out upfront. The ERG considers that it is more plausible to assume that patients treated in the subsequent-line would already have been tested for ALK and/or other mutations, so the cost of testing these patients need not be taken into account. The ERG also notes that there may be a discount available for upfront testing that has not been taken into account by the company
- The cost of treating pulmonary embolism may have been underestimated which affects the cost of treating AEs

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

Given the fundamental uncertainties in this appraisal, the ERG is not able to provide preferred base case ICERs per QALY gained. It has instead provided a number of individual revisions and scenario combinations that explore the sensitivity of the ICERs generated by the company models to alternative methods of estimating OS and utility values for PFS.

The ERG has amended estimates of OS in the first-line base case model to investigate the effects of two ERG assumptions: that the OS HR is equal to the PFS HR from the PROFILE 1014 trial; and that PPS is the same for treatment with crizotinib and treatment with pemetrexed+platinum. The ERG has investigated similar scenarios in the subsequent-line model: that the OS HR is equal to the PFS HR from the PROFILE 1007 trial (and is applied to estimates of crizotinib OS that are unadjusted for crossover instead of to RPSFTM-adjusted estimates of docetaxel OS); and that PPS is the same for treatment with crizotinib and treatment with docetaxel.

The ERG has investigated the impact of assuming that the different OS treatment effects explored in the base case models are also applicable in the PROFILE 1001 scenario, whilst using the company's own modelling of OS for treatment with crizotinib. The ERG has also remodelled the OS, PFS and TTD data from the PROFILE 1001 study as an alternative to the company's modelling of time-to-event data from that trial.

The ERG has explored the impact of using different PFS utility values in the first-line model to evaluate the possible effect of bias in the reporting of EQ-5D from the PROFILE 1014 trial. The ERG has investigated three scenarios for the first-line PFS utility values: both treatments have a PFS utility equal to treatment with crizotinib in the base case (0.81); both treatments have a PFS utility equal to treatment with pemetrexed+platinum in the base case (0.72); and treatment with pemetrexed+platinum has a PFS utility of 0.75 (versus 0.72 in the base case).

Finally, the ERG has investigated the effect of combining the time-to-event scenarios with the PFS utility scenarios in the appropriate treatment lines.

1.10.1 Cost effectiveness conclusions

The resulting ICERs per QALY gained in the first-line base case when applying the ERG's revisions individually and in combination vary from [redacted] to [redacted]. The resulting ICERs per QALY gained in the subsequent-line base case when applying the ERG's revisions individually and in combination vary from [redacted] to [redacted].

The resulting ICERs per QALY gained in the first-line PROFILE 1001 scenario when applying the ERG's revisions individually and in combination vary from [redacted] to [redacted]. The resulting ICERs per QALY gained in the subsequent-line PROFILE 1001 scenario when applying the ERG's revisions individually and in combination vary from [redacted] to [redacted].

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Sections B.1.3 and B.1.3.1 of the company submission (CS) include an overview of non-small cell lung cancer (NSCLC) and a description of ROS1+ advanced NSCLC. Key points from these sections of the CS are included as bulleted items in Box 1 and Box 2. The Evidence Review Group (ERG) considers that these points are largely accurate, but that they lack detail on the burden of ROS1+ advanced NSCLC experienced by patients, carers and society.

Box 1 Company overview of NSCLC

- Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases.[1] According to the National Lung Cancer Audit Report (2016),[2] 38,232 cases of lung cancer were reported in England and Wales in 2015.
- Lung cancer is often diagnosed at an advanced stage due to the low index of suspicion surrounding the symptoms or the presence of symptoms only at an advanced stage of the disease.[3] In England, 75.3% of lung cancer cases are diagnosed at an advanced stage of disease (21.4% and 53.9% for stages III and IV, respectively).[4] Due to late diagnosis, the prognosis for patients diagnosed with lung cancer is often poor.[5]
- Lung cancer can be categorised into two major types: small-cell lung cancer and non-small cell lung cancer (NSCLC).[2] NSCLC accounts for the majority (88% in England and Wales)[2] of lung cancer cases and can be sub-typed further into three histological types: adenocarcinoma (63.5% of NSCLC), large-cell undifferentiated carcinoma (4.2% of NSCLC) and squamous cell carcinoma (32.4% of NSCLC).[6] Both adenocarcinoma and large-cell undifferentiated carcinoma are classified as non-squamous histological sub-types of NSCLC.
- There are different molecular subtypes of lung cancer and there is a shift towards practising precision medicine with the availability of targeted therapies which can treat specific molecular subtypes of cancer. Targeted therapies are now the standard of care for patients with epidermal growth factor receptor (EGFR)-mutant or anaplastic lymphoma kinase-positive (ALK+) advanced NSCLC. ROS1+ advanced NSCLC is considered to represent another group of patients who would benefit from a targeted treatment option.

EGFR=epidermal growth factor receptor
Source: CS, pp19 and 20

Box 2 Company description of ROS1+ advanced NSCLC

- ROS1+ advanced NSCLC is estimated to occur in 1.1–1.8% of NSCLC patients and to be found almost exclusively in non-squamous tumours.[7-9] This incidence is considerably lower than tumours harbouring ALK, EGFR or Kirsten rat sarcoma viral oncogene homologue (KRAS) mutations, which account for between 3.4%, 15.3% and 32.6% of NSCLC, respectively.[6] This suggests that ROS1+ advanced NSCLC is rare in England and Wales. ROS1-translocations are usually mutually exclusive to other oncogenic drivers.[7,10]
- ROS1 was ….. identified as a key oncogenic driver in a number of other cancers, including NSCLC in 2007.[11] In lung cancer, there is no single most common fusion partner with ROS1, with several being described.[12] Different fusion partners are not thought to impact on the efficacy of crizotinib, as the ROS1 tyrosine kinase protein (and binding site for crizotinib) is consistent.[13] Inhibition of ROS1 is associated with anti-tumour activity in preclinical models, as demonstrated in both in vitro phenotypic assays and in vivo transgenic mouse and xenograft models. As in ALK, crizotinib, via inhibition of ROS1, has demonstrated dose-dependent inhibition of cell proliferation and induced apoptosis in cell-based assays, as well as dose-dependent tumour regression in in vivo xenograft models.[14,15]

- The clinical and pathologic features of ROS1+ tumours have been characterised, with ROS1-positivity showing associations with non-smoker status and a younger age of diagnosis.[14] In addition, ROS1-translocations are almost exclusively detected in non-squamous tumour types, and predominantly in adenocarcinoma tumour types.[14] NSCLC associated with an underlying ROS1 gene-rearrangement is, however, fundamentally different from unselected NSCLC and unselected adenocarcinoma, as disease progression in ROS1+ NSCLC patients is dependent on the activated ROS1 receptor tyrosine kinase (RTK).[11,16] Similarly, the clinical benefit of specific targeted therapies, such as crizotinib, is dependent on the role of the activated ROS1 RTK in driving cancer progression.[11,16]

EGFR=epidermal growth factor receptor; RTK=receptor tyrosine kinase
Source: CS, p20

In Section B.1.3.1 of the CS (CS, p20), the company compares ROS1+ and anaplastic lymphoma kinase-positive (ALK+) advanced NSCLC (Box 3).

Box 3 Company comparison of ROS1+ and ALK+ NSCLC

- The ROS1 oncogene encodes an orphan RTK related to ALK.[17] In both ROS1+ and ALK+ NSCLC the genetic translocation events lead to gene fusions that result in deregulated expression of the respective kinase domain, ALK or ROS1, with constitutive activation of the kinase activity.[11,16,18,19] This oncogene activation event means that ROS1+ and ALK+ NSCLC are fundamentally different from unselected NSCLC and unselected adenocarcinoma, as disease progression is dependent on these activated RTKs.[11,16]

- The kinase domains of ALK and ROS1 share 77% amino acid identity within the adenosine triphosphate-binding sites, and crizotinib binds with high affinity to both ALK and ROS1, as expected based on their homology.[20] This was recognised by the EMA as supporting the biology of ALK and ROS1 fusions in NSCLC as being analogous.[14]

- As with ALK+ NSCLC patients, patients with ROS1+ NSCLC patients are usually non-smokers or light smokers, predominantly have histologic features of adenocarcinoma and are young.[7,21] A small proportion of patients in both the ROS1+ and ALK+ NSCLC populations have demonstrated sensitivity to pemetrexed-based chemotherapy, providing further evidence to support the similarities between these two populations.[18] These similarities were supported and validated by leading UK clinical experts.[22]

EMA=European Medicines Agency; RTK=receptor tyrosine kinase
Source: CS, p20

The ERG agrees with the company that ROS1+ and ALK+ advanced NSCLC are different diseases from undifferentiated NSCLC. The ERG accepts the company's view (supported by 12 UK clinicians who attended the company's advisory board meeting[22]) and the opinion of the European Medicines Agency[14] (EMA), that biological and clinical similarities exist between ROS1+ and ALK+ advanced NSCLC and that there are similarities between patients with ROS1+ and ALK+ advanced NSCLC. However, the ERG notes that the incidence of ROS1+ advanced NSCLC is low (between 1% and 2% of NSCLC tumours)[7] and that, throughout the CS, the company refers to ROS1+ advanced NSCLC as an 'ultra-orphan disease' (e.g. CS, pp20-21, p54, p81, p85). Clinical advice to the ERG is that the small numbers of patients with ROS1+ advanced NSCLC thus far identified does not allow robust comparisons to be made between the outcomes from patients with ROS1+ and ALK+ advanced NSCLC who are treated with crizotinib.

The company puts forward the case that clinical evidence data derived from randomised controlled trials (RCTs) of patients with ALK+ advanced NSCLC are an appropriate proxy for clinical data from patients with ROS1+ advanced NSCLC (Box 4).

Box 4 Company rationale for the relevance of data from trials of patients with ALK+ advanced NSCLC

- Given the similarities between ROS1+ and ALK+ advanced NSCLC patients, data from randomised controlled trials of crizotinib in ALK+ advanced NSCLC patients are deemed relevant to the clinical efficacy and safety of crizotinib in ROS1+ patients. The PROFILE 1007[23-28] trial provided evidence for the approval of crizotinib for previously treated ALK+ advanced NSCLC by the EMA and NICE,[29,30] and the PROFILE 1014[31-34] trial provided data on the activity of crizotinib in the approval of crizotinib for first-line ALK+ advanced NSCLC.[35,36] As such, the data from the PROFILE 1007[23-28] and 1014[31-34] trials in ALK+ advanced NSCLC has been deemed suitable by clinical experts[22] as an appropriate proxy for ROS1 and will be used where data for crizotinib versus a comparator in ROS1+ advanced NSCLC are limited..

EMA=European Medicines Agency
Source: CS, p20

Throughout the CS, the company states that the generalisability of data from ALK+ advanced NSCLC patients to ROS1+ advanced NSCLC patients was strongly supported by the 12 leading UK experts who attended the company's advisory board meeting.[22] The company also states that the EMA considered the clinical evidence from trials in the ALK+ advanced NSCLC population when granting the marketing authorisation[14] for the use of crizotinib in patients with ROS1+ advanced NSCLC. The ERG notes that the opinion given in the clinical expert statement[37] submitted to NICE on behalf of The British Thoracic Oncology Group, The National Cancer Research Institute, The Royal College of Physicians and The Association of Cancer Physicians, is that patients with ROS1+ and ALK+ advanced NSCLC are clinically similar, and that it is reasonable to generalise outcomes from the ALK+ population to the ROS1+ population.

Clinical advice to the ERG is that it is uncertain if the currently documented similarities between ROS1+ and ALK+ advanced NSCLC will be supported as more patients with ROS1+ advanced NSCLC are identified. The ERG questions whether the evidence thus far available allows the outcomes from patients with ALK+ advanced NSCLC to be robustly generalised to patients with ROS1+ advanced NSCLC.

The ERG notes that the data presented in the CS in support of the clinical effectiveness of crizotinib in patients with ROS1+ advanced NSCLC are derived from a single-arm study, known as the PROFILE 1001[13,38-42] study. The study recruited 53 patients with ROS1+ advanced NSCLC, 7 of the patients had untreated disease and 46 patients had received 1 (or more) prior treatments. The results of the PROFILE 1001 study were the basis for the EMA European marketing authorisation[14] and for the Food and Drug Administration (FDA) approval

in the US of the use of crizotinib in the treatment of ROS1+ advanced NSCLC. The ERG notes that the EMA[14] has acknowledged that ROS1+ is a rare form of NSCLC and, that therefore, the current evidence base for ROS1+ NSCLC is immature. In particular, the EMA highlighted in the European Public Assessment Report[14] (EPAR) that the prognosis for patients with ROS1+ NSCLC is unknown as the evidence available is limited to the results of a small number of retrospective studies, with some that have contradictory results. The EMA concluded that '…benefit of a therapy selectively addressing patients with ROS1+ NSCLC is at present not fully evaluable' EPAR, p42).[14]

It is highlighted in the CS (CS, p26, p29, p31, p54) that data are unlikely to ever be available from an RCT of crizotinib conducted in patients with ROS1+ advanced NSCLC. Clinical advice to the company (CS, p26, p29, p31, p54) is that given the small number of patients with ROS1+ advanced NSCLC and the clinical efficacy of crizotinib as demonstrated in the PROFILE 1001 study, clinical equipoise would not be feasible and, therefore, it would be unethical to conduct an RCT in this patient population.

The company's case for the clinical and cost effectiveness of the use of crizotinib in the treatment of patients with ROS1+ advanced NSCLC rests on the assumption that RCT data derived from patients with ALK+ advanced NSCLC can be used as proxy data for the ROS1+ advanced NSCLC patient population.

2.2 Critique of company's overview of current service provision

An overview of current service provision is presented in Section B.1.3.2 of the CS. The company expects that crizotinib will be used in place of non-targeted chemotherapy treatments in the untreated and subsequent treatment settings.

The company presents a treatment algorithm outlining the existing treatment pathway for patients with advanced NSCLC (Figure 1). The company has referred to relevant published NICE guidance in footnotes in the CS. The company correctly points out (CS, p23) that, at present, there are no recommended treatments for patients with ROS1+ advanced NSCLC and, that testing for ROS1 is not carried out routinely in the NHS. However, the company anticipates (CS, p23) that, with the advent of routine testing for ROS1 NSCLC, crizotinib will be mostly used to treat previously untreated patients.

The ERG considers that the algorithm presented by the company largely reflects current clinical practice and would capture the treatment pathway if crizotinib were recommended by NICE for use in patients with ROS+ advanced NSCLC in the NHS. The ERG notes that in the

first-line setting, NICE also recommends single agent third-generation chemotherapy for patients who cannot tolerate platinum-based chemotherapy (not shown in algorithm).[43]

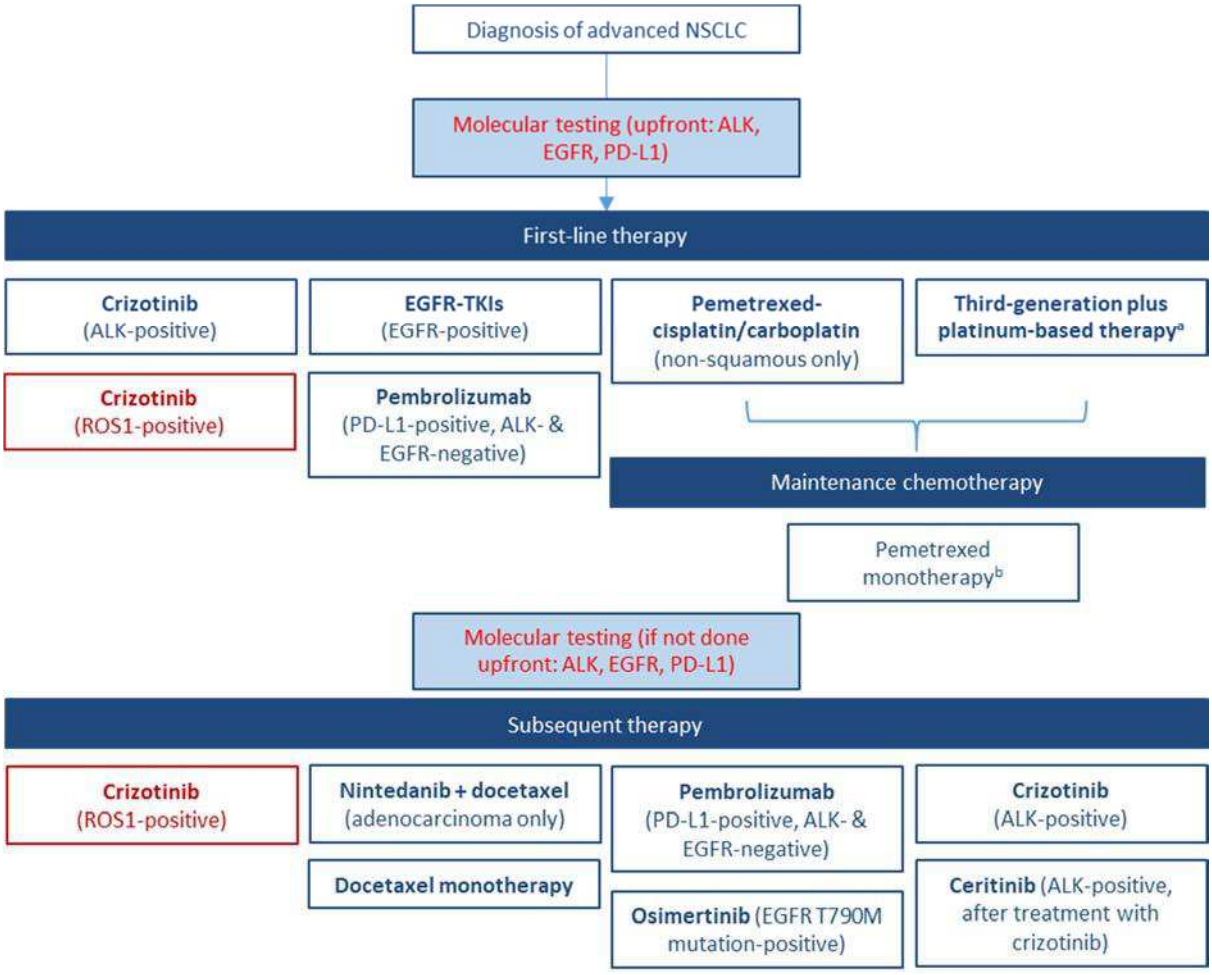


Figure 1 NHS treatment algorithm presented by the company

Source: CS, Figure 2

2.3 Summary of relevant clinical guidance and guidelines

In the footnotes of the treatment algorithm presented in the CS, the company has included references to relevant published guidance and treatment guidelines for NSCLC, however, no further details are provided. A summary of the available NICE guidelines[43] and published guidance[15,30,44-55] for the treatment of NSCLC is presented in Table 1.

The ERG notes that crizotinib is currently recommended by NICE for use in patients with untreated ALK+ advanced NSCLC (TA406)[36] and for patients with previously treated ALK+ advanced NSCLC (TA422).[30]

Table 1 ERG summary of published NICE guidelines and guidance

NICE guideline or guidance	Summary of NICE recommendations
Guideline	
Lung cancer: diagnosis and management CG121[43] (2011)	• For patients with tumours of negative or unknown EGFR status and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) chemotherapy should be offered; where the chemotherapy should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) • Patients who are unable to tolerate combination therapy may be offered single-agent chemotherapy with a third-generation drug
First-line treatment	
TA181[45] (2009)	• **Pemetrexed in combination with cisplatin**: if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma
TA192[47] (2010)	• **Gefinitib**: patients whose tumours test positive for EGFR tyrosine kinase mutation
TA258[48] (2012)	• **Erlotinib**: patients whose tumours test positive for EGFR tyrosine kinase mutation
TA310[49] (2014)	• **Afatinib**: patients whose tumours test positive for EGFR tyrosine kinase mutation
TA406[15] (2016)	• **Crizotinib**: patients whose tumours test positive for ALK mutation

TA447[55] (2017)	• **Pembrolizumab** is recommended for use within the Cancer Drugs Fund as an option for untreated PD-L1-positive metastatic non-small-cell lung cancer in adults, only if:
	  • their tumours express PD-L1 with at least a 50% tumour proportion score and have no EGFR- or ALK+ mutations
	  • pembrolizumab is stopped at 2 years of uninterrupted treatment and no documented disease progression
	  • the conditions in the managed access agreement for pembrolizumab are followed

Maintenance treatment	
TA190[46] (2010)	• **Pemetrexed**: patients with other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel
TA402[53] (2016)	• **Pemetrexed**: patients with non-squamous disease whose disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and who have an ECOG PS 0 or 1 at the start of maintenance treatment
Second-line treatment	

TA374[44] (2015)	• **Erlotinib** is an option for patients who have:
	  • had non-targeted chemotherapy because of delayed confirmation that their tumour is EGFR-TK mutation-positive
	  • progressed after non-targeted chemotherapy and who have tumours of unknown EGFR-TK mutation status, but only if the result of an EGFR-TK mutation diagnostic test is unobtainable because of an inadequate tissue sample or poor-quality DNA; the treating clinician considers that the tumour is very likely to be EGFR-TK mutation-positive; and there is an observed response within the first 2 cycles of treatment

TA395[51] (2016)	• **Ceritinib**: adults with advanced ALK+ disease who have previously received crizotinib
TA347[50] (2015)	• **Nintedanib+docetaxel**: for patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy,
TA416[52] (2016)	• **Osimertinib**: patients with EGFR T790M mutation-positive disease whose disease has progressed after first-line treatment with an EGFR-TK inhibitor (only available via the CDF)
TA422[30] (2016)	• **Crizotinib:** previously treated adults with ALK+ NSCLC (after a rapid re-review by the CDF)
TA428[54] (2017)	• **Pembrolizumab:** patients with PD-L1 positive NSCLC in adults who have had at least one prior chemotherapy (and EGFR/ALK targeted treatment, if relevant) if treatment is stopped at 2 years of uninterrupted treatment and no documented disease progression

CDF=Cancer Drugs Fund; DNA=Deoxyribonucleic acid; ECOG=Eastern Co-operative Oncology Group; EGFR=epidermal growth factor receptor; EGFR TK=epidermal growth factor receptor tyrokinase; PD-L1=programmed death ligand 1; WHO=World Health Organisation

2.4 Testing for ROS1 status in the NHS

In the summary of product characteristics (SmPC)[56] for crizotinib, it is stipulated that treatment should only be initiated after the patient's ROS1 status is positively confirmed by a clinical laboratory test using a validated test method. The company discusses the issues relevant to testing for ROS1 NSCLC within the NHS (CS, p25).

The company states that testing for ROS1 status is not generally available in the NHS and is not part of routine clinical practice. The ERG understands that the main methods of testing for ROS1 status are immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH) testing. Clinical advice to the company (CS, p25) is that IHC testing followed by a confirmatory FISH test is considered optimal; however, next generation sequencing (NGS) may be routinely available within the NHS in the future.

The company reports that strategies for testing for ROS1 positivity in NHS patients are in development in some NHS laboratories. The company describes two possible testing strategies, the first is to test for ROS1 positivity in patients with non-squamous NSCLC at the same time that tests for epidermal growth factor receptor (EGFR) and ALK positivity are conducted. The second strategy is to test for ROS1 positivity only after tumours are confirmed to be negative for EGFR and ALK NSCLC. The company states that a working group of pathologists, sponsored by Pfizer Ltd, recommended that testing for ROS1 positivity is carried out at the same time as other molecular tests and that this approach is also included in published expert recommendations.[57] The company points out (CS, p27) that if the sequential testing strategy (as discussed in Section 2.3.1 of this ERG report) for the identification of ROS1+ advanced NSCLC is adopted in the NHS, there is the potential for a delay in the diagnosis and treatment of patients.

2.5 Innovation

The company puts forward the case that crizotinib is an innovative treatment (CS, p78). The company states that:

- Crizotinib is the only available targeted treatment for ROS1+ advanced NSCLC that is licensed in Europe and the UK
- The FDA granted crizotinib "Breakthrough Therapy designation" and "Priority Review"[58]
- The EMA granted a marketing authorisation for crizotinib based on the results of a single-arm study[14]

- Crizotinib is an oral treatment and is therefore more convenient and less onerous compared with intravenously administered treatment options

- Treatment with crizotinib is associated with considerable treatment benefits for patients with ROS1+ advanced NSCLC compared with treatment with chemotherapy.

The ERG agrees that crizotinib is the only targeted treatment for ROS1+ advanced NSCLC that is licensed in Europe and the UK and, that compared with treatment with chemotherapy, oral treatment is more convenient and less onerous.

2.6 Number of patients eligible for treatment with crizotinib

The company estimates that 289 patients will be diagnosed with ROS1+ advanced NSCLC annually in England and Wales. The company's estimate, presented in the 'Budget Impact' section of Document A of the CS, is based on an incidence rate of 1.7% in patients with non-squamous disease.

The ERG's own estimate of the number of patients who are likely to be diagnosed with ROS1+ NSCLC in England and Wales and who may be eligible for treatment with crizotinib is presented in Table 2. The ERG estimate of 274 is consistent with the company's estimate of 289 patients. The ERG is uncertain how many of the patients currently being treated in the NHS are likely to be identified as having ROS1+ advanced NSCLC.

Table 2 ERG estimation of number of patients eligible for treatment with crizotinib in England and Wales annually

Parameter	Data source	Percentage	Number of patients
Percentage of cases of lung cancer in 2015	National Lung Cancer Audit Report[2]		38,232
Percentage of patients with non-squamous NSCLC	Clinical Lung Cancer Genomics Project[6]	67.7%	25,883
Percentage of patients diagnosed with advanced lung cancer (England) in 2014	National Lung Cancer Audit Report[2] Stage IIIb and Stage IV	59%	15,271
Percentage of patients with ROS1+ advanced NSCLC	Scheffler[9]	1.8%	274

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

A summary of the decision problem outlined in the final scope issued by NICE[59] and that addressed in the CS is presented in Table 3. Each parameter in Table 3 is discussed in more detail in the text following the table.

Table 3 Comparison between NICE scope and company decision problem

Final scope issued by NICE **Parameter and specification**	**Decision problem addressed in the company submission**
Population: People with ROS1+ advanced NSCLC	People with ROS1+ advanced NSCLC. However, with the exception of the 53 patients with ROS1+ advanced NSCLC, all of the data discussed in the CS are derived from patients with ALK+ advanced NSCLC.
Intervention: Crizotinib	Crizotinib
Comparators <u>Untreated disease</u> • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) with a platinum drug (carboplatin or cisplatin) - With (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) - With (following cisplatin containing regimens only) or without pemetrexed maintenance treatment • Single agent chemotherapy with a third-generation drug for people who cannot tolerate platinum-based therapy <u>After previous chemotherapy treatments</u> • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care	Pemetrexed+platinum (data are derived from patients with ALK+ advanced NSCLC) Docetaxel monotherapy (data are derived from patients with ALK+ advanced NSCLC who received either pemetrexed or docetaxel monotherapy)
Outcomes • OS • PFS • RR • AEs • HRQoL	PFS, RR and AEs presented for the population and intervention in the final scope issued by NICE Comparative clinical effectiveness analyses presented are based on data evaluating the use of crizotinib in ALK+ advanced NSCLC patients as a proxy for ROS1+ advanced NSCLC patients
Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any PAS for the intervention or comparator technologies will be taken into account The use of crizotinib is conditional on ROS1+ status. The economic modelling should include the costs associated with diagnostic testing for ROS1 status in people with advanced non-small cell lung cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals	Economic analysis based on data evaluating the use of crizotinib in ALK+ advanced NSCLC patients as a proxy for data from ROS1+ advanced NSCLC patients Data from PROFILE 1001 study evaluating the use of crizotinib in ROS1+ advanced NSCLC patients used in a scenario analysis An agreed PAS is in place for crizotinib for the treatment of patients with ALK+ advanced NSCLC. The PAS will be extended to the ROS1+ advanced NSCLC indication if the treatment is recommended for this group of patients The company did not provide a sensitivity analysis without the cost of the diagnostic test
Subgroups to be considered: None specified	None identified
Special considerations: None specified	None identified

AE=adverse event; HRQoL=health-related quality of life; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; RR=response rate

3.1 Clinical effectiveness evidence presented in the company submission

The only clinical effectiveness data available for the ROS1+ advanced NSCLC population are from the PROFILE 1001, single-arm study. The study recruited 53 patients, 7 patients with untreated disease and 46 patients who had received one or more prior chemotherapies. The overall survival (OS) data from the PROFILE 1001 study are, at present, immature (median OS is not reached). This means that there are no median OS data for patients with ROS1+ advanced NSCLC who have been treated with crizotinib.

The ERG notes that the EMA's marketing authorisation for crizotinib for the treatment of ROS1+ advanced NSCLC is based on the outcomes of the 53 patients recruited to the PROFILE 1001 study. The ERG also notes from the EPAR[14] for crizotinib that the EMA considered the data for the efficacy of crizotinib for patients treated at first-line (n=7) were 'limited'. However, the EMA noted that the results of the PROFILE 1001 study of crizotinib in patients with untreated ALK+ advanced NSCLC were supported by the subsequent PROFILE 1014[31-34] trial (crizotinib versus pemetrexed+platinum in patients with untreated ALK+ advanced NSCLC). The EMA concluded that similarities between ROS1+ and ALK+ advanced NSCLC are sufficient to assume that crizotinib would also be clinically effective in the first-line treatment of ROS1+ advanced NSCLC.[14]

There is no direct clinical evidence comparing crizotinib for the treatment of patients with ROS1+ advanced NSCLC in any setting with any of the comparators listed in the final scope issued by NICE. To compare crizotinib with pemetrexed+platinum in an untreated patient population and docetaxel in a previously treated population, the company has provided evidence from a patient population not specified in the final scope issued by NICE, i.e. patients with ALK+ advanced NSCLC. The company's economic base case incorporates the outcomes of patients with ALK+ advanced NSCLC in the PROFILE 1014 and PROFILE 1007 RCTs.

The PROFILE 1014 trial was designed to compare the clinical effectiveness of crizotinib with pemetrexed+platinum in patients with previously untreated ALK+ advanced NSCLC. The PROFILE 1007 trial was designed to compare the clinical effectiveness of crizotinib with chemotherapy (pemetrexed or docetaxel) in patients with previously treated ALK+ advanced NSCLC.

Clinical advice to the ERG is that it is too early to be certain if the data from trials in patients with ALK+ advanced NSCLC can be used as proxy data for patients with ROS1+ advanced NSCLC (see Section 2.1 of this ERG Report).

The ERG considers that the company has met the criteria stipulated in the decision problem in the final scope issued by NICE, **only** if it is accepted that the outcomes from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC.

3.2 Population

The population described in the final scope issued by NICE is people with ROS1+ advanced NSCLC. The population discussed in the CS is the population recruited to the PROFILE 1001 study, which is identical to the population described in the final scope issued by NICE. However, the ERG notes that the direct evidence presented in the CS for the use of crizotinib in patients with ROS1+ advanced NSCLC is from a small, single-arm study (PROFILE 1001).

Most of the evidence presented in the CS is proxy evidence derived from two RCTs conducted in patients with ALK+ advanced NSCLC. The ERG considers that the company has met the population parameter specified in the decision problem only if the outcomes from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC.

Treatment line is not specified either in the final scope issued by NICE or in the EMA licence. The company expects that crizotinib will be used as a first- and subsequent-line treatment. However, the company anticipates that the number of patients treated at subsequent-line will reduce over time as more patients with advanced ROS1+ advanced NSCLC are identified at initial diagnosis and treated with crizotinib in the first-line (CS, p25).

The trial centres in the PROFILE 1001 study were based in the USA, Australia and South Korea. None of the trial centres were based in the UK. Clinical advice to the ERG is that patients recruited to the PROFILE 1001 study are broadly comparable to patients with ROS1+ advanced NSCLC who are likely to be treated in the NHS, with the proviso that the patients recruited to the trial are younger and fitter and have fewer co-morbidities than NHS patients. Clinical advice to the ERG is that, as crizotinib is a targeted treatment in a mutation-driven subtype cancer, patients in the NHS are likely to achieve similar response rates and disease control regardless of these differences.

The company considers that data derived from the PROFILE 1014 and PROFILE 1007 trials in patients with ALK+ advanced NSCLC provide appropriate proxy data for patients with ROS1+ advanced NSCLC. The ERG notes that, compared with patients in the PROFILE 1014 and PROFILE 1007 trials, patients recruited to the PROFILE 1001 study were older, heavier

and were more likely to have never smoked. In addition, patients in the PROFILE 1001 study were fitter than patients in the PROFILE 1014 trial.

The company's rationale for and the ERG's comments on this assumption are discussed in Section 2.1 of this ERG Report. In summary, the ERG is uncertain whether there is enough evidence at present for conclusions to be drawn regarding similarities between these conditions and to allow robust comparisons to be made between the clinical efficacy of crizotinib for treating patients with ROS1+ and ALK+ advanced NSCLC.

3.3 Intervention

The intervention identified in the final scope issued by NICE is crizotinib. Crizotinib is a small molecule inhibitor of receptor tyrosine kinase (RTK) and is selectively active against RTKs associated with ROS1, ALK, hepatocyte growth factor receptor (HGFR) and Recepteur d'Origine Nantais (RON). Crizotinib is licensed in Europe for i) the treatment of ROS1+ advanced NSCLC[14] and ii) the treatment of ALK+ advanced NSCLC.[29,35]

Crizotinib is available as a hard capsule (200 mg or 250 mg). The daily dose is 500 mg (250 mg twice daily).

3.4 Comparators

The comparators in the final scope issued by NICE vary by line of treatment, i.e. untreated or previously treated disease. In the absence of RCT evidence from patients with ROS1+ advanced NSCLC, the company has used clinical evidence from two RCTs conducted in patients with ALK+ advanced NSCLC.

Data available to the company for the clinical efficacy of crizotinib in patients with ALK+ advanced NSCLC were limited to two RCTs i.e., the PROFILE 1014 trial and the PROFILE 1007 trial. The company has presented the results from the PROFILE 1014 and PROFILE 1007 trials in narrative form.

3.4.1 Comparators addressed in the company submission

Untreated disease (PROFILE 1014)

Pemetrexed+platinum. The company has provided clinical effectiveness evidence for the comparison of crizotinib with pemetrexed+platinum. Clinical advice to the company (CS, p25) is that, in the UK, patients with ROS1+ advanced NSCLC who are fit enough to be treated with chemotherapy would be treated with pemetrexed+platinum. The ERG agrees with the company that pemetrexed+platinum is recommended by NICE in TA181[45] for treating patients with non-squamous NSCLC. The ERG notes that current knowledge of ROS1+ NSCLC

suggests that most ROS1+ tumours are of adenocarcinoma (and therefore of non-squamous) histology.

The company has presented evidence from the PROFILE 1014 trial in which patients with ALK+ advanced NSCLC who had not received previous systemic treatment were randomised to receive either crizotinib or pemetrexed+platinum chemotherapy.

After previous chemotherapy (PROFILE 1007)

Docetaxel. The company has provided clinical effectiveness evidence for the comparison of crizotinib with docetaxel. The evidence for the effectiveness of docetaxel is derived from the PROFILE 1007 trial in which patients with advanced ALK+ NSCLC who had received up to three lines of previous systemic treatment were randomised to receive either crizotinib or either pemetrexed or docetaxel monotherapy. The ERG notes that in the UK, NICE recommends[50] docetaxel+nintedanib as a treatment for patients with tumours of adenocarcinoma histology that have progressed after first-line chemotherapy. Clinical advice to the ERG is that docetaxel monotherapy is also used to treat patients who are not fit enough for treatment with docetaxel+nintedanib. The ERG notes that pemetrexed monotherapy is not listed as a comparator in the final scope issued by NICE and it is not used in UK clinical practice to treat patients with previously treated NSCLC.

3.4.2 Comparators not addressed in the company submission

The company discusses (CS, p25 to p27) issues relevant to the comparators not addressed in the CS (Table 4 and Table 5).

Table 4 Comparators not addressed in the company submission (untreated disease)

Comparator	Company rationale for exclusion	ERG comment
Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) +platinum with or without pemetrexed maintenance treatment Single agent chemotherapy with a third-generation drug for people who cannot tolerate platinum-based chemotherapy	• Following consultation with UK clinical experts, it was noted that first-line docetaxel, paclitaxel or vinorelbine are rarely used in patients with non-squamous disease in the first-line setting. These are instead comparators more commonly used to treat patients with squamous disease. It is also understood that gemcitabine is not commonly used in patients with non-squamous disease, however may be an alternative therapy offered to a small number of patients with non-squamous disease who are not able to tolerate pemetrexed-platinum doublet therapy This approach was also used for the NICE appraisal of crizotinib for untreated ALK+ NSCLC (TA406[15]) • As ROS1 mutation-rearrangements are fundamentally different from the oncogenic drivers in unselected NSCLC, efficacy data for first-line docetaxel, gemcitabine, paclitaxel or vinorelbine in unselected NSCLC is not deemed applicable in the ROS1+ advanced NSCLC population. Therefore, there are no data to form a reliable comparison to first-line docetaxel, gemcitabine, paclitaxel or vinorelbine, and as such it has not been addressed in the decision problem	The ERG agrees that in clinical practice in the UK, patients with tumours of non-squamous histology are unlikely to be treated with platinum based chemotherapy treatment plus docetaxel, gemcitabine, paclitaxel or vinorelbine The ERG notes that in TA406, the company submission discussed patients with tumours of adenocarcinoma histology as most ALK+ NSCLC tumours are of adenocarcinoma histology (approximately 98%) The ERG agrees that ROS1+ NSCLC is different to unselected NSCLC and that there is no clinical effectiveness evidence for the use of third-generation chemotherapies specific to patients with ROS1+ advanced NSCLC
Pemetrexed maintenance treatment (for patients with non-squamous NSCLC)	• Clinical experts have suggested that approximately 15% of patients with advanced NSCLC would be eligible for pemetrexed maintenance after platinum doublet first-line chemotherapy, based on fitness. Given the small proportion of patients who receive maintenance therapy, this was not considered as a comparator in this submission • The exclusion of this comparator is in line with the final NICE scope for crizotinib for untreated ALK+ NSCLC • Furthermore, there is insufficient evidence on the efficacy of pemetrexed maintenance in patients with ROS1+ NSCLC, and the data available from the ALK+ NSCLC population is from a mixed chemotherapy comparator (pemetrexed plus platinum followed by pemetrexed maintenance/ASCEND-4)	The ERG agrees that approximately 15% of patients with advanced NSCLC are likely to receive pemetrexed maintenance after platinum doublet first-line chemotherapy The ERG notes that pemetrexed maintenance therapy was not a listed comparator in the final scope issued by NICE for TA406 The ERG notes that the ASCEND-4 RCT compares the clinical efficacy of ceritinib versus pemetrexed+platinum in patients with advanced ALK+ NSCLC. In the ASCEND-4 trial, 127 of 175 patients treated with pemetrexed+platinum continued treatment with pemetrexed maintenance therapy. Subgroup data from the ASCEND-4 trial are not available

Table 5 Comparators not addressed in the company submission (previously treated disease)

Comparator	Company rationale for exclusion	ERG comment
Docetaxel with (for adenocarcinoma histology) nintedanib	• Data for nintedanib with docetaxel were only available from the broader unselected NSCLC population, with subgroup analysis for patients with adenocarcinoma, and not from the ROS1+ NSCLC population. As ROS1 mutation-rearrangements are fundamentally different from the oncogenic drivers in unselected NSCLC or unselected adenocarcinoma,[11,16] the efficacy data from the unselected NSCLC population (including unselected adenocarcinoma) is not deemed applicable to the ROS1+ NSCLC population • No data in the proxy ALK+ NSCLC population exists for nintedanib with docetaxel	The ERG agrees that ROS1+ NSCLC is different to unselected NSCLC and unselected adenocarcinoma and that there are no data relevant to patients with ROS1+ advanced NSCLC and that there are also no data relevant to patients with ALK+ advanced NSCLC However, the ERG considers that docetaxel+nintedanib is standard of care for patients with tumours of adenocarcinoma histology and has more favourable outcomes than docetaxel monotherapy
BSC	• Data for BSC as a subsequent-line option in patients who have received upfront chemotherapy are only available in the unselected NSCLC population and not from the ROS1+ advanced NSCLC population. As ROS1 mutation-rearrangements are fundamentally different from the oncogenic drivers in unselected NSCLC, efficacy data for BSC in unselected NSCLC is not deemed applicable in the ROS1+ NSCLC population. Therefore, there are no data to form a reliable comparison to BSC, and as such it has not been addressed in this decision problem. This aligns with comments from the ERG where the mixed treatment comparison to BSC was criticised for lacking robustness due to key differences between the selected and unselected patient populations. (TA296[60] and TA422[30]) • Furthermore, patients with ROS1+ NSCLC are typically young and otherwise fit enough for chemotherapy, and as such BSC is likely to be used in a smaller proportion of patients with ROS1+ NSCLC compared to patients with unselected NSCLC	The ERG agrees that there are no data available to compare crizotinib with BSC, in either patients with ROS1+ NSCLC or ALK+ NSCLC The ERG notes that the mixed treatment comparison presented in the TA296 and TA422 was not considered by the AC to be robust as it included patients with unselected NSCLC The ERG agrees that patients with ROS1+ NSCLC are likely to be fit for further treatment

3.5 Outcomes

Outcome data for patients with ROS1+ advanced NSCLC are available from the PROFILE 1001 study. Data are presented in the CS for the outcomes of progression-free survival (PFS) and adverse effects of treatment (AEs). Several measures of response rate (RR) are also presented, including objective response rate (ORR), disease control rate (DCR), duration of response (DR) and time to tumour response (TTR). Immature data (30% at the time of the 2014 analysis) for OS are presented in the CS; however, median OS was not reached and the company does not intend to carry out further updates of OS until [redacted]. No health-related quality of life (HRQoL) data were collected during the PROFILE 1001 study.

Outcome data for patients with untreated ALK+ advanced NSCLC are available from the PROFILE 1014 trial. Data are presented in the CS for the outcomes of PFS, ORR, AEs and HRQoL. Data for OS are also presented (44.3% mature) however, median OS was not

reached and data are confounded by crossover. This means that the true OS associated with crizotinib in patients with untreated ALK+ advanced NSCLC is unknown.

Outcome data for patients with previously treated ALK+ advanced NSCLC are available from the PROFILE 1007 trial. Data are presented in the CS for the outcomes of PFS, ORR, AEs and HRQoL. Data for OS are also presented (69.8% mature); however, the ERG notes that high levels of crossover were allowed in the trial. This means that the true OS associated with crizotinib in patients with previously treated ALK+ advanced NSCLC is unknown.

Limitations of the overall survival data presented by the company

The ERG notes that there are no mature OS data available for patients with ROS1+ advanced NSCLC. The ERG also notes that the OS data from patients with ALK+ advanced NSCLC presented in the CS, i.e. the PROFILE 1014 and PROFILE 1007 trials, are immature and problematic. This means that there are no useful OS data for either the population specified in the decision problem (i.e. people with ROS1+ advanced NSCLC) or for the ALK+ advanced NSCLC population used in the CS to mitigate the uncertainty around the limited data available for the population specified in NICE's decision problem.

3.6 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 20-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS and Personal Social Services perspective. The evidence for the company's base case is derived from two RCTs that were conducted in patients with ALK+ advanced NSCLC, the PROFILE 1014 and 1007 trials. The company has used data from the PROFILE 1001 study of patients with ROS1+ advanced NSCLC in a scenario analysis. The company considers that the use of the data from the PROFILE 1014 and PROFILE 1007 trials reduces the uncertainty associated with the small dataset available from the PROFILE 1001 study of patients with ROS1+ advanced NSCLC.

3.7 Equality considerations

In the SmPC for crizotinib, it is stipulated that treatment should only be initiated after the patient's ROS1 status is positively confirmed by a clinical laboratory test using a validated test method. The ERG notes that there is currently no routinely funded testing for ROS1 in the NHS. The company points out (CS, p27) that, if the sequential testing strategy (as discussed in Section 2.3.1 of this ERG report) for the identification of ROS1+ advanced NSCLC is adopted in the NHS, there is the potential for a delay in the diagnosis and treatment of patients.

The existing PAS agreement in place for crizotinib for the treatment of ALK+ advanced NSCLC[15,30] will be extended to include the ROS1+ advanced NSCLC patient population if crizotinib is recommended by NICE for this group of patients.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The CS adequately describes the search strategies used to identify relevant studies relating to the use of crizotinib for the treatment of patients with ROS1+ advanced NSCLC. The company conducted a systematic search for clinical effectiveness evidence and separate systematic searches were conducted for the retrieval of cost effectiveness studies, HRQoL studies and cost and healthcare resource identification studies.

The ERG notes that the company has used the results from trials of patients with ALK+ advanced NSCLC who were treated with crizotinib as proxy data for patients with ROS1+ advanced NSCLC. The company has not reported if systematic searches were conducted to identify relevant studies relating to the use of crizotinib for the treatment of patients with ALK+ advanced NSCLC.

Searches for evidence indexed in electronic databases

Full details of the search terms used to locate clinical evidence are reported in the CS (Section B.2 and Appendix D). The company states that they searched the following databases: MEDLINE, MEDLINE in Process, EMBASE (all via OvidSP) and The Cochrane Library (limited to the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Database Abstracts of Reviews of Effects). Searches were run from database inception to 16 March 2017 and animal studies were removed. The company searches did not include drug-related search terms (i.e. crizotinib, Xalkori); however, the searches did include relevant and comprehensive disease terms, which means that despite the searches being broad, it is unlikely any relevant papers would have been missed by the omission of the drug-related terms. No clinical trial registries were searched, possibly resulting in relevant trials being missed.

Overall, the ERG considers that the strategies used to search the electronic databases are appropriate and are adequately described in the CS. The ERG has run its own searches and is confident that no relevant publications have been missed.

Searches for evidence presented at conferences

In addition to searches of bibliographic databases, the company also conducted hand searches of six conference sites on 1 June 2017: American Society of Clinical Oncology (ASCO), European Lung Cancer Conference (ELCC), European Society for Medical Oncology (ESMO), International Society for Pharmacoeconomics and Outcomes Research (ISPOR),

International Association for the Study of Lung Cancer and the Italian Association of Medical Oncology's National Congress of Medical Oncology. The keywords for these searches are included in the CS and are relevant. The company states that the searches of conference proceedings were limited to those published between 2015 and 2017. The company assumed that older, pre-2015 conference abstracts would be published as full-text articles in peer reviewed journals. The ERG considers that the hand searches for evidence presented at conferences are appropriate and adequately described in the CS.

The data sources searched and the time spans for the searches are provided in Table 6. A summary of, and ERG comments on, the review methods used by the company are presented in Table 7.

Table 6 Data sources for the clinical systematic review

Search strategy component	**Source**	**Search date range**	
		Start	**End**
Electronic database searches	EMBASE	From inception	March 2017
	MEDLINE		
	MEDLINE In-Process		
	Cochrane Central Library of Controlled Trials (CENTRAL)		
Congress proceedings	American Society of Clinical Oncology (ASCO) European Lung Cancer Conference (ELCC) European Society for Medical Oncology (ESMO) International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International Association for the Study of Lung Cancer Italian Association of Medical Oncology's National Congress of Medical Oncology	2015	2017
Clinical trial registries	ClinicalTrials.gov	Not searched	
	WHO's meta-registry 'International Clinical Trials Registry Platform Search Portal' (ICTRP)		
	EU Clinical Trial Registry		

EU=European Union; WHO=World Health Organisation
Source: CS, Appendix D

Table 7 Summary of, and ERG comment on, the systematic review methods used by the company

Review method	Results	ERG comment
Searching		
Sources searched: • Electronic databases • Congress proceedings • Clinical trial registries	512 non-duplicate titles	• The search was carried out in March 2017 meaning that there is a risk that some relevant studies may not have been included in the search results • Clinical trial registries were not searched. However, details of ongoing trials were presented • Reference lists of identified studies were searched for other relevant studies
Formal eligibility criteria		
Two analysts independently assessed study eligibility based on the criteria presented in Table 4 of Appendix D of the CS (p14), i.e. Patients: ROS1+ advanced or metastatic NSCLC Intervention: crizotinib, docetaxel (with or without nintedanib), nivolumab, pembrolizumab or pemetrexed Comparator: any or no comparator Study type: RCT, interventional clinical trial or observational study	14 unique studies from 28 publications	• Use of two independent assessors improves the quality of the review
Additional eligibility criteria		
Search limits		The searches were restricted to studies published in English language. Relevant non-English language studies were not included
Quality assessment		
The company assessed the risk of bias of the non-randomised studies using the Downs and Black checklist.[61] The risk of bias of the RCTs presented by the company to provide comparative data for the clinical effectiveness of crizotinib was assessed using the criteria specified by the Centre for Reviews and Dissemination at the University of York.[62] The results of the company's assessment of risk of bias are presented in Tables 11, 12 and 13 of Appendix D of the CS		

Source: CS, Appendix D

4.1.2 Evidence synthesis

The company presents direct evidence to support the clinical efficacy of crizotinib for the treatment of ROS1+ advanced NSCLC from one single-arm study, PROFILE 1001. The company identified 13 other non-randomised studies that included patients with ROS1+advanced NSCLC (CS, p31). The company has provided details of the 13 studies in Table 7 of the CS. The company has provided full study information in the appendices to the CS.

Nine of the identified studies included crizotinib as the intervention. Four were prospective, single-arm, phase II studies: AcSé,[63] EUCROSS,[64] METROS[65] and OX-ONC.[66] The EUCROSS[64] and METROS[65] studies were conducted in European centres and the OX-ONC[66]

study was conducted in centres in East Asia. The ERG notes that only the EUCROSS[64] and OX-ONC[66] studies are complete.

The company has presented data from the EUCROSS[64] study (n=34) in support of the results from the PROFILE 1001 study. The company states (CS, p31) that the EUCROSS[64] study was conducted in European patients and the results are therefore applicable to patients treated in the NHS. The company states (CS, p31) that data from the EUCROSS[64] study are not included in the submitted economic model as Kaplan-Meier (K-M) curves for PFS and OS were not available at the time the submission was prepared; however, the company provided the K-M curves via the clarification process.

The company does not consider that the results of the OX-ONC[66] study are generalisable to a UK population (CS, Table 7) and has not included the results in the clinical- or cost-effectiveness section of the CS. The ERG notes that a substantial number of patients (n=127) were recruited to the OX-ONC[66] study; however, all patients in the OX-ONC[66] study were of East Asian origin and their results may be not be applicable to a UK patient population.

The company reports that the EUROS,[10] Bennati,[67] Lu[68] and Zhang[69] studies were small, retrospective studies of patients treated with crizotinib for ROS1+ advanced NSCLC and that the studies reported by Chen,[70] Drilon,[71] Liang[72] and Song[73] were small, retrospective studies of patients with ROS1+ advanced NSCLC who were treated with pemetrexed-based chemotherapy. The company has not included the results of the retrospective studies in the clinical or cost effectiveness section of the CS. The ERG agrees that this is appropriate. The study by Oz[74] was a subgroup analysis of results from five patients located in Turkey who were recruited to the PROFILE 1001 expansion study.

In the absence of any evidence for the efficacy of crizotinib in the treatment of ROS1+ advanced NSCLC with other comparators listed in the final scope issued by NICE, the company presents the data from two RCTs conducted in patients with ALK+ advanced NSCLC i.e., the PROFILE 1014 and the PROFILE 1007 trials. The PROFILE 1001 study and the PROFILE 1014 and 1007 trials are described narratively in the CS.

4.2 ERG critique of clinical effectiveness evidence

4.2.1 Identified studies and trials

Pivotal study

The PROFILE 1001 study is a single-arm, phase I study, which provides evidence to support the use of crizotinib to treat ROS1+ advanced NSCLC.

Supportive trials

The company states (CS, p26) that, given the efficacy of crizotinib in patients with ROS1+ advanced NSCLC, as demonstrated by the results of the PROFILE 1001 study, clinical experts to the company consider that it would be unethical to conduct comparative trials due to the lack of clinical equipoise. Clinical equipoise exists when there is no good basis for a choice between two or more treatment options.[75] Consequently, no comparative trials have been conducted to investigate the effectiveness of crizotinib in the ROS1+ advanced NSCLC population. The company presents data from the PROFILE 1014 and PROFILE 1007 trials, which investigated the efficacy of crizotinib in comparison to chemotherapy in patients with ALK+ advanced NSCLC, to support the claim that crizotinib is a clinically effective treatment for patients with ROS1+ advanced NSCLC. The company's rationale for this approach is discussed in Section 2.1 of this ERG report.

Other non-randomised studies identified in the company's systematic review

The company identified 13 non-randomised studies in their systematic review. The company considers that the studies provide limited clinical data describing crizotinib and/or chemotherapy for the treatment of ROS1+ advanced NSCLC. Since these studies are not used to provide estimates of clinical or cost effectiveness, the ERG does not provide a full description and critique of these studies in the subsequent sections. However, the ERG has summarised the key findings from these studies and discussed whether data from these studies support the use of crizotinib to treat ROS1+ advanced NSCLC in Section 4.6 of this report.

4.2.2 Key characteristics of the included study and trials

Key characteristics of the pivotal PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials are provided in Table 8.

Table 8 Key characteristics of the included study and trials

	PROFILE 1001	PROFILE 1014	PROFILE 1007
Location	International: 8 locations across USA, Australia and South Korea	International: 251 locations across USA, Canada, Mexico, Australia, Asia, Europe (9 UK sites), South America and South Africa	International sites in North America, Australia, Brazil, China, Japan, Korea, Taiwan, Hong Kong and Europe (9 UK sites)
Study design	Multicentre, open-label, single-arm, phase I study. Initial dose-escalation phase followed by an expansion phase in ROS1+ advanced NSCLC patients (n=53)	Multicentre, open-label, phase III randomised controlled trial (n=343) Patients in the chemotherapy group who had PD defined using RECIST v1.1, as verified by IRR, could cross over to crizotinib treatment if the safety criteria were met	Multicentre, double-blind, phase III randomised, controlled clinical trial (n=347) Patients in the chemotherapy group who had PD defined using RECIST could cross over to crizotinib treatment as part of a separate study
Population	Adult patients (≥18 years of age) with confirmed locally advanced, recurrent, or metastatic ROS1+ NSCLC (Three patients were included in the trial who were ALK- and retrospectively determined to be ROS1+)	Adult patients (≥18 years of age) with confirmed locally advanced, recurrent, or metastatic non-squamous NSCLC that was positive for an ALK rearrangement, who had not received previous treatment for advanced disease	Adult patients (≥18 years of age) with confirmed locally advanced, recurrent, or metastatic NSCLC that was positive for an ALK rearrangement, who had progressive disease only after one prior (platinum-based) chemotherapy regimen
Intervention and comparator	Intervention: crizotinib 250 mg twice daily Patients with RECIST-defined PD or clinical deterioration could continue on crizotinib treatment at the investigator's discretion and with the approval from the Sponsor Comparator: N/A	Intervention: crizotinib 250 mg twice daily Patients could continue crizotinib treatment beyond RECIST-defined PD, at the discretion of the investigator if the patient was perceived to be experiencing clinical benefit Comparator: pemetrexed, 500 mg/m^2 BSA, plus platinum-based therapy; iv administered every 3 weeks for a maximum of 6 cycles Platinum-based therapy consisted of either cisplatin, 75 mg/m^2 BSA, or carboplatin, target AUC of 5–6 mg/mL/min	Intervention: crizotinib 250 mg twice daily Comparator: docetaxel 75 mg/m^2 or pemetrexed 500 mg/m^2 BSA Patients could continue treatment as assigned beyond the time of RECIST-defined progression, as assessed by the IRR, at the discretion of the investigator if the patient was perceived to be experiencing clinical benefit
Reported outcomes specified in the scope	Primary outcome: ORR Secondary outcomes: OS, PFS, TTF, safety	Primary outcome: PFS Secondary outcomes: ORR, OS, safety, EQ-5D	Primary outcome: PFS Secondary outcomes: ORR, OS, safety, EQ-5D

ALK=anaplastic lymphoma kinase; AUC=area under the concentration-time curve; BSA=body surface area; EQ-5D=EurQoL-5 Dimensions; IRR=independent radiology review; iv=intravenous; N/A=not applicable; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; RECIST=response evaluation criteria in solid tumours; BSA=body surface area; TTF=time to treatment failure
Source: adapted from CS, Table 6 and Table 10, PROFILE 1014 CSR and PROFILE 1007 CSR

Further details of the methodology of the PROFILE 1001 study (including ROS1 testing methodology and treatment schedule) are provided in Table 8 of the CS. A comparative summary of the methodologies used in the PROFILE 1001 study and in the PROFILE 1014 and PROFILE 1007 trials (including eligibility criteria and concomitant medications) is provided in Table 10 of the CS.

The ERG is of the opinion that the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials were generally well designed and well conducted. The patient population recruited to the PROFILE 1001 study matches the patient population specified in the final scope issued by NICE. Clinical advice to the ERG is that the eligibility criteria used in the PROFILE 1001 study are appropriate. The main limitations of the PROFILE 1001 study are the small sample size (n=53) and the fact that there was no comparator arm to provide direct evidence of the effectiveness of crizotinib in comparison to a relevant comparator in the patient population of interest.

Both the PROFILE 1014 and PROFILE 1007 trials permitted patients to switch from the chemotherapy arm to the crizotinib arm on disease progression (and vice versa). Valid OS estimates for the efficacy of crizotinib versus chemotherapy are difficult to obtain due to high levels of patient crossover. Patient crossover in the PROFILE 1014 and PROFILE 1007 trials is discussed further in Section 4.3.2 of this ERG report.

4.2.3 Characteristics of patients in the included study and trials

The baseline characteristics of patients in the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials are provided in Table 9.

Table 9 Patient characteristics of the included study and trials

		PROFILE 1001 (ROS1+ safety population)	PROFILE 1014 (ALK+ ITT population)		PROFILE 1007 (ALK+ ITT population)	
		Crizotinib (N=53)	Crizotinib (N=172)	Chemotherapy (N=171)	Crizotinib (N=173)	Chemotherapy (N=174)
Age (years): median, (min, max)		55 (25–81)	52.0 (22–76)	54 (19–78)	51 (22–81)	49 (24–85)
Category (years) – no. (%)	<65	38 (71.7)	[redacted]	[redacted]	146 (84.4)	151 (86.8)
	≥65	15 (28.3)	[redacted]	[redacted]	27 (15.6)	23 (13.2)
Sex – no. (%)	Male	23 (43.4)	68 (39.5)	63 (36.8)	75 (43.4)	78 (44.8)
	Female	30 (56.6)	104 (60.5)	108 (63.2)	98 (56.6)	96 (55.2)
Race – no. (%)	White	30 (56.6)	91 (52.9)	85 (49.7)	90 (52.0)	91 (52.3)
	Black	2 (3.8)	[redacted]	[redacted]	2 (1.2)	3 (1.7)
	Asian	21 (39.6)	77 (44.8)	80 (46.8)	79 (45.7)	78 (44.8)
	Other	NR	4 (2.3)	2 (1.2)	2 (1.2)	2 (1.2)
Weight (kg)	Mean (SD)	71.9 (16.0)	[redacted]	[redacted]	65.3 (17.3)	[redacted]
	Median (range)	70.0 (48.0-106.3)	[redacted]	62.5 (35.8–151.6)[a]	62.0 (35.2-160.0)	[redacted]
ECOG performance status	0	23 (43.4)	[redacted]	[redacted]	72 (41.6)	65 (37.4)
	1	29 (54.7)	[redacted]	[redacted]	84 (48.6)	95 (54.6)
	2	1 (1.9)	9 (5.2)	[redacted]	16 (9.2)	14 (8.0)
Smoking status – no. (%)	Never smoker	40 (75.5)	106 (61.6)	112 (65.5)	108 (62.4)	111 (63.8%)
	Ex-smoker	13 (24.5)	56 (32.6)	54 (31.6)	59 (34.1)	54 (31.0%)
	Current smoker	NR	10 (5.8)	5 (2.9)	5 (2.9)	9 (5.2%)
Histological classification – no. (%)	Adenocarcinoma	51 (96.2)	158 (91.9)	159 (93.0)	163 (94.2)	160 (92.0%)
	Non-adenocarcinoma	2 (3.8)	14 (8.1)	12 (7.0)	9 (5.2)	14 (8.0)

		PROFILE 1001 (ROS1+ safety population)	PROFILE 1014 (ALK+ ITT population)		PROFILE 1007 (ALK+ ITT population)	
		Crizotinib (N=53)	Crizotinib (N=172)	Chemotherapy (N=171)	Crizotinib (N=173)	Chemotherapy (N=174)
Prior radiation therapies – no. (%)	No	34 (64.2)	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	19 (35.8)	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior systemic therapy regimens:	0	7 (13.2)	172 (100)	171 (100)	[redacted]	[redacted]
	1	20 (37.7)	0	0	[redacted]	[redacted]
	2	13 (24.5)	0	0	[redacted]	[redacted]
	3	3 (5.7)	0	0	[redacted]	[redacted]
	>3	10 (18.9)	0	0	[redacted]	0
	Not reported	0	0	0	[redacted]	0
Extent of disease[c]- no. (%)	Locally advanced	NR	4 (2.3)	3 (2)	7 (4.0)	8 (4.6%)
	Metastatic	NR	168 (97.7)	168 (98.2)	165 (95.4)	166 (95.4%)
Prior surgeries – no. (%)		53 (100)	NR	NR	NR	NR
Brain metastases present – no. (%)		NR	45 (26.2)	47 (27.5)	60 (35)	
Time since first diagnosis median		1.16 years (0.0 to 11.2)	1.2 months (0–114.0)	1.2 months (0–93.6)	[redacted]	[redacted]

[a] One person's weight incorrectly reported as 151.6kg instead of 151.6 pounds
[b] Two patients in the crizotinib group did not report their prior radiation therapy status
[c] Data missing for 4 patients in the crizotinib arm in the PROFILE 1007 trial
ALK=anaplastic lymphoma kinase; ECOG=Eastern Cooperative Oncology Group; ITT=intention to treat; NR=not reported; SD=standard deviation
Source: CS, Table 11

The ERG did not note any important differences in baseline characteristics between the treatment arms of the PROFILE 1014 and PROFILE 1007 trials.

The company presents results from the PROFILE 1014 and PROFILE 1007 trials (two ALK+ advanced NSCLC trials) as estimates of the effectiveness of treatment with crizotinib for ROS1+ advanced NSCLC patients in first-line and subsequent-line settings. The following two assumptions must hold for the company's approach to be valid:

1) ROS1+ advanced NSCLC and ALK+ advanced NSCLC patient populations must be comparable in terms of baseline characteristics

2) Patients recruited to the ALK+ advanced NSCLC trials must be representative of the ALK+ advanced NSCLC patient population (and consequently the ROS1+ advanced NSCLC patient population, if assumption 1 holds) that would be seen in NHS clinical practice.

For assumption 1, clinical advice to the ERG is that ROS1+ advanced NSCLC and ALK+ advanced NSCLC patient populations are comparable in terms of baseline characteristics.

For assumption 2, as noted in TA406, when the patient population in the PROFILE 1014 trial is compared with a 'real-life' cohort of ALK+ advanced NSCLC patients from the US and Canada,[76] the results suggest that the PROFILE 1014 trial patients are younger, have better performance status and are less likely to be smokers than the real-life patients. Furthermore, patients from a small UK retrospective cohort of ALK+ advanced NSCLC patients (details of which were provided by the company in their clarification response during TA406) were also older than the PROFILE 1014 population. In light of this information, the company performed adjustments to the PFS and OS data from the PROFILE 1014 trial that were used in the submitted economic model by incorporating the baseline characteristics from the 'real-life' cohort described by Davis et al.[76] These adjustments are discussed further in Section 5.4.5 of this ERG report. However, clinical advice to the ERG is that patients in the PROFILE 1001 study and patients in the PROFILE 1014 and 1007 trials have similar baseline characteristics and broadly represent patients likely to be treated in the NHS.

The estimates presented in the clinical effectiveness section of the CS (and in this ERG report) have not been adjusted to account for any differences between the patient characteristics of the PROFILE 1014 trial population and the cohort study described by Davis.[76] Clinical advice to the ERG is that patients recruited to the PROFILE 1014 trial are generally representative of patients treated in the NHS and the ERG questions the adjustments made in the company's

economic model. The ERG notes that the Appraisal Committee for TA406 considered that the adjustments were 'conservative'.

In TA296, no adjustments were performed on the PFS and OS data from the PROFILE 1007 trial as the ERG considered the patient population to be reflective of the patients with ALK+ advanced NSCLC in who would be treated in the NHS.

Prior therapy in the PROFILE 1001 study and the PROFILE 1007 trial

Most patients in the PROFILE 1001 study (n=46, 86.8%) and all patients in the PROFILE 1007 trial had received prior therapy for advanced disease. Clinical advice to the ERG is that all patients are offered pemetrexed as a first-line therapy in current NHS clinical practice. It is therefore informative to consider how many of the patients who received prior therapy in the PROFILE 1001 study and in the PROFILE 1007 trial received pemetrexed+platinum as a first-line treatment.

For the 46 pre-treated patients in the PROFILE 1001 study, only 17 (37.0%) received pemetrexed as a first-line treatment (company response to the ERG clarification letter, Table 2). In the PROFILE 1007 trial, [redacted] patients had received prior pemetrexed chemotherapy. Consequently, 63% of patients in the PROFILE 1001 study, and [redacted] of patients in the PROFILE 1007 trial, received first-line treatments that did not include pemetrexed+platinum and would not be commonly administered in NHS clinical practice.

4.2.4 Statistical approach adopted for the analysis of the included study and trials

In this section, the ERG provides a description and critique of the statistical approaches used to analyse data collected during the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials that relate to the outcomes stipulated in the final scope issued by NICE. Information relevant to the statistical approach taken by the company has been extracted from the trial protocols,[24,32,38] the trial statistical analysis plans (TSAPs),[23,31,39] the clinical study reports (CSRs),[26,33,41] and the CS. There is also a supplemental TSAP[40] for the PROFILE 1001 study that outlines the statistical analyses for the ROS1+ advanced NSCLC patient group and a preliminary CSR[25] for the PROFILE 1007 trial that includes the final results for several efficacy endpoints and patient-reported outcomes (PROs). The final CSR for the PROFILE 1007 trial presents the final analysis for OS, an update of the Visual Symptom Assessment Questionnaire-ALK (VSAQ-ALK) and an update of safety.

Analysis populations

The analysis populations used for the analyses in each of the included study and trials are provided in Table 47 (Appendix 10.1) of this ERG report. The ERG is satisfied that the analysis

populations were pre-specified in the TSAPs and that results for each outcome for the relevant populations were provided in the CSRs.

Efficacy outcomes

The definitions, assessment measures and statistical analysis methodology used for the primary outcomes of each of the included studies and trials are provided in Table 48 (Appendix 10.2) of this ERG report.

The ERG is satisfied that the definitions, assessment measures and statistical analysis methodology used for the primary outcomes of the included studies were pre-defined in the TSAPs.

OS and PFS were secondary efficacy outcomes of the PROFILE 1001 study. The definitions of OS, PFS, and other secondary efficacy outcomes are provided in Table 9 of the CS. Time-to-event data (OS, PFS, duration of response [DR], and time to progression [TTP] were analysed using the K-M method with 2-sided 95% confidence intervals (CIs) using the Brookmeyer-Crowley method.

OS and ORR were secondary outcomes of both the PROFILE 1014 and PROFILE 1007 trials. The definitions and methods of analysis for each of these outcomes were pre-specified in the TSAPs for each of the trials (PROFILE 1014: TSAP, pp13-14, pp23-25; PROFILE 1007: TSAP, p12, pp20-23). The ERG is satisfied that the results of all pre-planned efficacy analyses were reported in the CSRs.

The ERG notes that the Cox proportional hazards (PH) method was used to estimate the PFS and OS hazard ratios (HRs) for both the PROFILE 1014 and PROFILE 1007 trials. The validity of this method relies on the event hazards associated with the intervention and comparator data being proportional over time within each trial. The ERG assessed the validity of the PH assumption for all analyses provided in the CS that included a HR result (see Appendix 10.3 for methods and results). The ERG concluded that there is insufficient evidence to reject the PH assumption for the unadjusted OS and RPSFTM-adjusted (log-rank and Wilcoxon tests) OS data from the PROFILE 1014 trial, and for the unadjusted OS data from the PROFILE 1007 trial. The ERG did not assess PH for crossover-adjusted OS from the PROFILE 1007 trial, since the company used the PFS HR reported in the PROFILE 1007 trial to represent a crossover-adjusted OS HR (see Section 4.3.2 for further details of this approach). The ERG concluded that the PH assumption was not valid for PFS for either of the PROFILE 1014 or PROFILE 1007 trials. Consequently, the ERG considers that the reported HRs for PFS data from both the PROFILE 1014 and PROFILE 1007 trials should be interpreted with caution.

ERG critique of statistical approach

A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used to analyse data from the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials is provided in Table 49 (Appendix 10.4) of this ERG report.

Having carried out these checks, the ERG is satisfied with the pre-planned statistical approach employed by the company, with the exception that the Cox PH method was not suitable for the analyses of PFS data for either the PROFILE 1014 trial or for the PROFILE 1007 trial.

4.2.5 Risk of bias assessment of the included study and trials

The company assessed the quality of the PROFILE 1001 study using the Downs and Black checklist;[61] this is a risk of bias tool that can be used to assess non-randomised studies. The company's quality assessment is presented alongside the ERG's comments in Table 10. The company carried out quality assessments for the PROFILE 1014 and PROFILE 1007 trials using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal.[77] The company's risk of bias assessments for the PROFILE 1014 and PROFILE 1007 trials, and ERG comments, are presented in Table 11.

Overall, the ERG agrees with the company's assessment that the PROFILE 1001 study is a good quality study, and notes that, although the study was open-label, an analysis of ORR by independent radiology review (IRR) enables the robustness of the primary analysis to be verified, since assessments made by IRR would not be subject to detection bias. The ERG notes however, that the PROFILE 1001 study is a small, single-arm, phase I study.

The PROFILE 1014 and PROFILE 1007 trials also used open-label study designs. Assessments for the primary outcome and response-based secondary outcomes were made by IRR in both trials, so analyses of these endpoints would not be subject to detection bias. The results for subjective outcomes may be subject to bias since patients and care providers were not blinded. Furthermore, the TA406 ERG raised the issue that, as a result of the open-label nature of the trial, patients in the chemotherapy arm may have initiated second-line therapy (including switching to crizotinib) earlier in the PROFILE 1014 trial than they might have been able to do in NHS clinical practice. The ERG agrees with the TA406 ERG's assessment and considers that this may be an issue that also affects the interpretation of data from the PROFILE 1007 trial.

The ERG agrees with the company's assessment that both the PROFILE 1014 and the PROFILE 1007 RCTs are of good quality, although the ERG notes that a substantial amount

of HRQoL data (~84%) was missing for patients in the crizotinib arm of the PROFILE 1014 trial. This issue is discussed further in Section 5.6.3 of this ERG report.

Table 10 Quality assessment results for the PROFILE 1001 study

Company's QA of the PROFILE 1001 study		**ERG comment**
Reporting		
1. Is the hypothesis/aim/objective of the study clearly described?	Y	Agree
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Y	Agree
3. Are the characteristics of the patients included in the study clearly described?	Y	Agree
4. Are the interventions of interest clearly described?	Y	Agree
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N/A	Agree
6. Are the main findings of the study clearly described (This question does not cover statistical tests which are considered below)?	Y	Agree
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Y	Agree
8. Have all important adverse events that may be a consequence of the intervention been reported?	Y	Agree
9. Have the characteristics of patients lost to follow-up been described?	N	Agree - 1 patient was lost to follow-up so not concerning
10. Have actual probability values been reported (eg. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	N	Agree
External validity		
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	No	Unable to determine
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes	Unable to determine
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	No	Disagree
Internal validity - bias		
14. Was an attempt made to blind study subjects to the intervention they have received?	No	Agree
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	No (although IRR was conducted)	Agree
16. If any of the results of the study were based on "data dredging", was this made clear?	Yes	Unable to determine
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	N/A	Agree
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Agree

19. Was compliance with the intervention/s reliable?	Unable to determine	Agree
20. Were the main outcome measures used accurate (valid and reliable)?	Yes	Agree
Internal validity – confounding (selection bias)		
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A	Agree
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N/A	Agree
23. Were study subjects randomised to intervention groups?	No	Agree
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	No, study not randomised	Agree
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Unable to determine if an investigation of known confounders was performed but not reported	N/A (single-arm trial)
26. Were losses of patients to follow-up taken into account?	Yes	Agree
Power		
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes	Agree

IRR=independent radiology review; N/A=not applicable; QA=quality assessment
Source: CS Appendix D, Table 11; ERG comment

Table 11 Quality assessment results for the PROFILE 1014 and PROFILE 1007 trials

	PROFILE 1014		PROFILE 1007	
	Company's QA	**ERG comments**	**Company's QA**	**ERG comments**
Was randomisation carried out appropriately?	Yes	Agree	Yes	Agree
Was the concealment of treatment allocation adequate?	Unclear	Disagree - participants were randomised via IVRS/website and therefore allocation was concealed	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, for care providers and participants Yes, for outcome assessors	Agree – the ERG notes that the open-label nature of the trials provides an opportunity for subjective results to be biased	Blinding of patients and care providers was not feasible, as each treatment arm utilised different methods of drug administration Outcome assessors for the IRR were blind to treatment allocation	Agree – the ERG notes that the open-label nature of the trials provides an opportunity for subjective results to be biased
Were there any unexpected imbalances in drop‑outs between groups?	No	Agree for efficacy outcomes PROs and HRQoL information were missing for the crizotinib arm (~84%)	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree	Yes - some outcomes are not yet available from PROFILE 1007 trial	Agree – although this is not a concerning issue if results for these outcomes are published in due course. The ERG is not aware of any updated data
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree	Yes	Agree

HRQoL=health-related quality of life; IRR=independent radiological review; ITT=intention-to-treat; IVRS=interactive voice response system; PRO=patient-reported outcomes; QA-=quality assessment
Source: CS Appendix D, Table 12 and Table 13; ERG comment

4.3 Results of the included studies and trials

4.3.1 Results of the PROFILE 1001 study

The data cut-off date for the primary analysis of the PROFILE 1001 study was 30th November 2014; the median duration of follow-up for OS at this time was 25.4 months. The data cut-off date for the ALK-negative (ALK-) patients who were retrospectively defined to be ROS1+ (n=3) was 24th June 2014. A summary of efficacy results for the PROFILE 1001 study is provided in Table 12.

Table 12 Summary of efficacy results from the PROFILE 1001 study

Outcome		PROFILE 1001 (N=53)
ORR based on investigator assessment	ORR (%) (95% CI)	37 (69.8) [55.7 to 81.7]
	Complete response (%)	5 (9.4)
	Partial response (%)	32 (60.4)
	SD (≥6 weeks) (%)	11 (20.8)
	PD (%)	3 (5.7)
	Early death (%)	1 (1.9)
	Indeterminate (%)	1 (1.9)
ORR based on IRR (n=50)	ORR (%) (95% CI)	33 (66.0) [51.2 to 78.8]
	Complete response (%)	1 (2.0)
	Partial response (%)	32 (64.0)
	SD (≥6 weeks) (%)	12 (24.0)
	PD (%)	4 (8.0)
	Early death (%)	1 (2.0)
	Indeterminate (%)	0 (0.0)
DCR	DCR at Week 8 (%) (95% CI)	46 (86.8) [74.7 to 94.5]
	DCR at Week 16 (%) (95% CI)	42 (79.2) [65.9 to 89.2]
DR (n=37[a])	Median months (range)	NR (15.2 to NR)
TTR (n=37[a])	Median weeks (range)	7.9 (4.3 to 32.0)
PFS	Patients with event (%)	26 (49.1)
	Median months (95% CI)	19.3 (14.8 to NR)
TTP	Patients with event (%)	23 (43.4)
	Median months (95% CI)	19.8 (15.2 to NR)
TTF	Median months (95% CI)	23.2 (15.0 to NR)
OS	Median months	NR
	HR (95% CI, p-value)	N/A
	Probability of survival at 6 months (95% CI)	90.6% (78.8 to 96.0)
	Probability of survival at 12 months (95% CI)	79.0% (65.3 to 87.8)
	Median duration of follow up months (95% CI)	25.4 (22.5 to 28.5)

[a] objective responders only
CI=confidence interval; DCR=disease control rate; DR=duration of response; IRR=independent radiology review; HR=hazard ratio; N/A=not available; NR=not reported; ORR=objective response rate; OS=overall survival; PD=progressed disease; PFS=progression-free survival; SD=stable disease; TTF=time to treatment failure; TTP=time to tumour progression; TTR=time to tumour response
Source: CS, Table 14

For ORR based on investigator assessment, the majority of patients achieved either a partial or complete response with crizotinib. Of the seven treatment-naïve patients, six achieved an objective response (85.7%, 95% CI: 42.1 to 99.6) compared to 31 out of 46 (67.4%, 95% CI: 52.0 to 80.5) patients who had received one or more prior therapies in the advanced setting. The company provides a plot showing individual patient responses to crizotinib in terms of percentage decrease or increase in tumour size from baseline in Figure 3 of the CS.

The ORR based on investigator assessment and the ORR based on IRR were similar, with a total event agreement rate between the derived-tumour assessment and IRR of 82.0%.

Median PFS was 19.3 months (95% CI: 14.8 to not reported [NR]), with 27 censored patients (50.9%), and 21 patients (39.6%) still on follow-up for disease progression on the data cut-off date. The company provides a K-M plot of PFS in Figure 5 of the CS. On the data cut-off date, three (42.9%) of the seven previously untreated patients had experienced an event (n=2 with objective progression, n=1 death without objective progression). Amongst previously treated patients (n=46), 23 patients (50.0%) had experienced an event by the data cut-off date (n=21 with objective progression, n=2 death without objective progression).

Median OS was not reached by the time of data cut-off, at which time 16 deaths had been recorded and 37 patients were censored. The company provides a K-M plot of OS in Figure 7 of the CS.

Inclusion of ROS1 negative patients in the PROFILE 1001 study

All patients underwent local diagnostic testing for ROS1 rearrangements; 51 of the 53 patients were diagnosed as having ROS1+ advanced NSCLC by FISH, while the remaining two patients were diagnosed as ROS1+ by reverse transcriptase polymerase chain reaction (RT-PCR). Available tissues samples (n=37 from 36 patients) were retrospectively tested for ALK rearrangement. Two patients were subsequently shown to be ROS1 negative by NGS (one of whom was also ALK+). Data from these two patients were kept in the analysis, as the trial protocol specified patients' gene translocations to be classified according to local testing (initial testing). The company discusses the impact of the inclusion of data from these two patients, concluding that the inclusion of data from these two patients was a conservative approach, since the outcomes for these patients were worse than or comparable to the outcomes reported for the whole trial population in terms of ORR, PFS and OS. [redacted]. The PFS durations of these patients were [redacted] (ALK-) and [redacted] (ALK+), respectively. The OS was [redacted] for the ROS1 negative, ALK- patient, whilst the OS was censored at [redacted] for the ROS1 negative, ALK+ patient. The ERG agrees with the company's

assessment that the inclusion of patients with ROS1 negative advanced NSCLC in the analyses was a conservative approach, and would not have biased the outcomes in favour of crizotinib.

Data immaturity

At the time of the PFS analysis, OS data from the PROFILE 1001 study were immature with only 30% of patients having died at the latest data cut-off date. The company states in their response to the ERG's clarification that the next data-cut for the PROFILE 1001 study is planned for [redacted]. No explanation as to why there is a 10-year gap in the timing of OS analyses was provided; the ERG notes that reliable estimates of OS from the PROFILE 1001 study will not be available until this time.

4.3.2 Results from the PROFILE 1014 and PROFILE 1007 trials

A summary of the key efficacy results from the PROFILE 1014 and PROFILE 1007 trials is provided in Table 13.

Table 13 Summary of the key efficacy results from the PROFILE 1014 and PROFILE 1007 trials

Outcome	PROFILE 1014 (N=343)	PROFILE 1007 (N=347)
Median PFS		
Crizotinib, months (95% CI)	10.9 (8.3 to 13.9)	7.7 (6.0 to 8.8)
Chemotherapy, months (95% CI)	7.0 (6.8 to 8.2)	3.0 (2.6 to 4.3)
HR, (95% CI; p-value)	0.45 (0.35 to 0.60; p<0.001)[a]	0.487 (0.371 to 0.638; p<0.0001)
Patients who crossed-over		
Crizotinib	33/172 (19.2%)	65/173 (37.6%)
Chemotherapy	[redacted]	151/174 (86.8%)
ORR[b]		
Crizotinib, no. of patients (%) [95% CI][c]	128 (74.4) [67.2 to 80.8]	112 (65.3) [57.7 to 72.4]
Chemotherapy, no. of patients (%) [95% CI][c]	77 (45) [37 to 53]	34 (19.5) [13.9 to 26.2]
Median OS		
Crizotinib, months (95% CI)	[redacted]	21.7 (18.9 to 30.5)
Chemotherapy, months (95% CI)	[redacted]	21.9 (16.8 to 26.0)
Unadjusted HR, (95% CI, p-value)	[redacted]	0.854 (0.66 to 1.10; p=0.11)
Crossover adjusted HR, (95% CI, p-value)	[redacted]	0.49 (0.37 to 0.64)

[a]For between-group comparisons (crizotinib vs chemotherapy), 2-sided log-rank test stratified according to baseline stratification factors were used; stratified Cox regression models were applied to estimate HRs
[b]Tumour response was assessed using RECIST v1.1 for the PROFILE 1014 and PROFILE 1007 trials and were confirmed by IRR
[c]P<0.001 for between-group comparison
CI=confidence interval; HR=hazard ratio; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria on Solid Tumours
Source: CS, Table 15

The ORRs for patients in the crizotinib arms of the PROFILE 1014 and PROFILE 1007 trials were comparable with the observed ORR for patients in the PROFILE 1001 study. Both the PROFILE 1014 and PROFILE 1007 trials demonstrated a statistically significantly greater ORR for crizotinib patients than for chemotherapy patients.

Median PFS data for crizotinib were not similar between the PROFILE 1001 study (19.3 months, 95% CI: 14.8 to NR) and the PROFILE 1014 and PROFILE 1007 trials (10.9 months, 95% CI: 8.3 to 13.9, and 7.7 months, 95% CI: 6.0 to 8.8, respectively). The ERG notes that the CIs for the estimates of median PFS do not overlap, so median PFS is statistically significantly longer for crizotinib patients with ROS1+ advanced NSCLC in the PROFILE 1001 study than for crizotinib patients with ALK+ advanced NSCLC in the PROFILE 1014 and PROFILE 1007 trials. The differences in median PFS between the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials causes the ERG to question whether the ALK+ and ROS1+ advanced NSCLC patient populations are truly similar, as discussed in Section 2.1 of this ERG report. In both the PROFILE 1014 and PROFILE 1007 trials, PFS was statistically significantly longer for crizotinib patients in comparison to chemotherapy patients.

Since median OS was not reached at the time of data cut-off in the PROFILE 1001 study, it is not possible to compare the OS results between the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials. Results for OS (unadjusted for patient crossover) from the PROFILE 1014 and PROFILE 1007 trials suggest that there are no statistically significant differences between crizotinib and chemotherapy in each of these trials. However, crossover-adjusted HR results from the PROFILE 1014 and PROFILE 1007 trials suggest that crizotinib statistically significantly improves OS in comparison to chemotherapy in ALK+ advanced NSCLC patients. A critique of how the company generated these crossover-adjusted HRs is provided in the subsequent sections of this ERG report.

Patient crossover in the PROFILE 1014 trial

The number of patients crossing over from the chemotherapy arm to the crizotinib arm and vice versa in the PROFILE 1014 trial is provided in Table 13.

At the time of the first data cut for OS analysis (30 November 2013), the rank preserving structural failure time model (RPSFTM), the iterative parameter estimation (IPE) and the two-stage method were applied to adjust for treatment switching from the chemotherapy arm to the crizotinib arm (but not to adjust for treatment switching from the crizotinib arm to the chemotherapy arm). The RPSFTM and the IPE methods are randomisation-based methods for estimating survival times that would have been observed in the absence of crossover. The two methods are similar; however, the IPE method requires the additional assumption that

survival times follow a parametric distribution. The company states that given the similarity between the methods and the almost identical results at the time of first OS analysis, the IPE model was not implemented at the time of the final analysis.

Furthermore, the company states that results of the two-stage method performed at the time of the first OS analysis were comparable to the results of the RPSFTM and IPE methods. However, the company explains that, for the two-stage method to provide a valid estimate of crossover-adjusted OS, it must be assumed that the post-progression survival (PPS) of non-crossover patients is representative of the PPS that crossover patients would have experienced had they not crossed over. At the time of the final OS analysis, a very small number of chemotherapy patients had disease progression who did not crossover to the crizotinib arm. The company explains that the uncertainty associated with treatment effect estimates derived using this methodology may be high and that the two-stage method was considered inappropriate for the final data cut of the PROFILE 1014 trial due to the high level of patient crossover.

Therefore, at the time of the final OS analysis, only the RPSFTM method was performed. Data used in the final OS analysis were adjusted for crossover from the chemotherapy arm to the crizotinib arm, and vice versa. The ERG assumes that, at the time of the final analysis, the company adjusted for crossover in both directions because in TA406, the company was criticised for only adjusting for crossover from the chemotherapy arm to the crizotinib arm.[36] Adjusted survival times were estimated using two variations of the RPSFTM method; log-rank and Wilcoxon (see Table 13 for results). The ERG is satisfied with the company's rationale for not implementing both the IPE and two-stage method at the time of the final OS analysis.

However, the ERG is also unsure whether the RPSFTM method is appropriate for adjusting for crossover, since the RPSFTM, and indeed the IPE, assumes a "common treatment effect", i.e., that the treatment effect received by patients who switch must be the same as the treatment effect received by patients initially randomised to the experimental group. The ERG notes that it is unclear whether this assumption would hold since patients randomised to pemetrexed+platinum who switch to crizotinib may, at that time, have more advanced disease than patients who were originally randomised to crizotinib; the patients randomised to pemetrexed+platinum, therefore may not have the same capacity to benefit from crizotinib treatment following disease progression as patients randomised to crizotinib. The ERG recognises that it is not possible to test the "common treatment effect" assumption, and that, in practice, this assumption is highly unlikely to ever be exactly true.

The ERG considers that the RPSFTM-adjusted HR for OS is unlikely to be valid, since the HR for RPSFTM-adjusted OS suggests an even greater benefit with crizotinib treatment than the PFS HR, suggesting that patients experience more benefit from treatment with crizotinib post-progression, than pre-progression.

In summary, the ERG considers that there is no method of adjusting for treatment switching that the ERG can confidently conclude would generate unbiased OS risk estimates for crizotinib versus chemotherapy for patients in the PROFILE 1014 trial. The ERG considers that the crossover-adjusted OS results presented for the PROFILE 1014 trial in Table 13 should be interpreted with caution.

Patient crossover in the PROFILE 1007 trial

The number of patients crossing over from the chemotherapy arm to the crizotinib arm and vice versa in the PROFILE 1007 trial is provided in Table 13.

For the PROFILE 1007 trial, the company estimates the crossover-adjusted OS HR to be 0.49 (95% CI: 0.37 to 0.64), without any explanation of how this crossover-adjusted HR was calculated. In TA422, the company submitted OS evidence using the RPSFTM crossover adjustment method to adjust survival times for patients in the chemotherapy arm. In TA422, the company also assessed the feasibility of the inverse probability of treatment and censoring weighted (IPTCW) method and the inverse probability of censoring weights (IPCW) methods. The company observed that the number of patients in the chemotherapy group who did not switch was too low for these methods to generate valid estimates of survival, since these methods use patients from the control group that never switched to create a counterfactual control group.

In TA422, the company presented three sets of crossover-adjusted OS results using the RPSFTM method with three different tests of equality, the log-rank, Wilcoxon and Cox model-based Wald tests. The TA422 ERG was concerned that the company did not report the CI of the estimated acceleration factor and also, that the company did not provide sufficient information regarding the estimation procedure of the RPSFTM method. The TA422 ERG concluded that the estimates of the treatment effect of crizotinib obtained by implementing the RPSFTM method should be considered highly uncertain.

In the absence of any exploration by the company of alternative methods to generate crossover-adjusted estimates of OS, the TA422 ERG considered two alternative ways of estimating the OS HR for use in cost effectiveness scenario analyses. The first approach was to use the same HR for OS as was reported in the original trial publication for PFS (HR=0.49,

95% CI: 0.37 to 0.64), and the second was to use the same HR for OS as per the crossover-adjusted OS HR reported for crizotinib versus pemetrexed+platinum patients in the PROFILE 1014 trial (at the time of the first OS analysis: HR=0.60, 95% CI: 0.27 to 1.42), estimated using the RPSFTM method with the Wilcoxon test. The TA422 Appraisal Committee preferred the TA422 ERG's first scenario (with an OS HR of 0.49) because it used data from the PROFILE 1007 trial and the HR for PFS was not confounded by crossover. The ERG assumes that it is for this reason that the company chose to present the PFS HR as a proxy for the true OS HR for the PROFILE 1007 trial in the current appraisal.

The rationale for adopting the TA422 ERG's first scenario (equal PFS and OS HRs) was that generally (although not universally) HRs for OS are normally not greater than HRs for PFS. Furthermore, the TA422 ERG referred to an analysis by the FDA[78] which explored trial-level and patient-level associations between PFS and OS in 14 advanced NSCLC trials (including crizotinib). A relationship between PFS and OS was not established at the trial-level, with the authors indicating that this was possibly because of crossover and longer survival after progression in the targeted therapy and first-line trials. However, in the patient-level responder analyses of the 14 trials, the same HR was reported for both PFS and OS (PFS: HR=0.40, 95% CI, 0.38 to 0.42; OS: HR=0.40, 95% CI, 0.38 to 0.43). The ERG agrees with the TA422 ERG that it is preferable to use the PFS HR as a proxy for the OS HR, instead of using the RPSFTM-adjusted OS HR, since the RPSFTM-adjusted HR demonstrates a greater treatment benefit with crizotinib than the PFS HR, suggesting that patients experience more benefit from treatment with crizotinib post-progression, than pre-progression. However, the ERG also notes that the true OS HR could be less than the PFS HR, and so the quoted HR for "crossover-adjusted" OS should be interpreted with caution.

At a late stage in the STA process, the company provided a crossover-adjusted OS HR for the PROFILE 1007 trial (HR=0.38; 95% CI 0.28 to 0.52), but without any detail of how this HR was calculated. The ERG notes that the HR does not match the RPSFTM-adjusted OS HR presented by the company in TA422, and so the ERG cannot comment on the validity of this HR. The ERG recommends that this estimate is interpreted with caution.

Proportional hazards

As previously discussed in Section 4.2.4 of this ERG report, the ERG concluded that the PH assumption was not valid for PFS data from the PROFILE 1014 or PROFILE 1007 trials. Consequently, the ERG considers that the reported HRs for PFS data from both the PROFILE 1014 and PROFILE 1007 trials and the reported "crossover-adjusted" OS HR for the PROFILE 1007 trial (which is actually the PFS HR from the same trial) should be interpreted with caution.

Inclusion of pemetrexed patients in the PROFILE 1007 trial comparator arm

The results presented in the CS from the PROFILE 1007 trial incorporate data from all patients in the chemotherapy arm, regardless of whether they received docetaxel (the company's comparator of interest for the second-line and later-line patient population) or pemetrexed. In the company's response to the ERG clarification letter, the company provided key results for the PROFILE 1007 trial stratified by type of chemotherapy administered in the comparator treatment arm, as provided in Table 14 of this ERG report.

The ORR of patients treated with docetaxel was lower ([redacted]) than the ORR of patients treated with pemetrexed ([redacted]), suggesting that patients treated with pemetrexed responded better than patients treated with docetaxel. Patients treated with docetaxel also had a numerically shorter PFS than patients treated with pemetrexed. The company states that, since patients in the PROFILE 1007 trial performed better with pemetrexed than docetaxel, the use of results from the pooled chemotherapy arm is a conservative approach, as it overestimates the treatment effect of docetaxel on OS. The ERG agrees with the company that it is highly likely that the inclusion of pemetrexed patients in the comparator arm would be a conservative approach when estimating the effectiveness of crizotinib in comparison to chemotherapy. However, the ERG also notes that docetaxel is not the standard NHS treatment option in this setting, most patients are treated with docetaxel+nintedanib which is more effective than docetaxel monotherapy.

Table 14 Key clinical efficacy results from the PROFILE 1007 trial stratified by type of chemotherapy received in the comparator treatment arm

Outcome	Crizotinib (N=172)	Pemetrexed (N=99)	Docetaxel (N=72)
Tumour response, ORR			
No. of patients (%) [95% CI]	[redacted]	[redacted]	[redacted]
RR, crizotinib vs comparator (95% CI; p-value)		[redacted]	[redacted]
PFS			
PFS, median (95% CI)	[redacted]	[redacted]	[redacted]
HR, crizotinib vs comparator (95% CI; p-value)		0.59 (0.43–0.80; p<0.001)[34]	0.30 (0.21 to 0.43; p<0.001)[34]
OS			
OS, median (95% CI)	[redacted]	[redacted]	[redacted]
HR (not adjusted for crossover), crizotinib vs comparator (95% CI; p-value)		0.901 (0.667 to 1.216; p=0.25)	0.791 (0.563 to 1.111; p=0.09)

CI=confidence interval; HR=hazard ratio; NR=not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RR=relative risk; vs=versus
Source: Company response to ERG clarification letter, Table 3

4.4 Health-related quality of life

The company states (CS, p65) that HRQoL data were not collected during the PROFILE 1001 study. This means that there are no direct HRQoL data for patients with ROS1+ advanced NSCLC.

The company has summarised the HRQoL data collected during the PROFILE 1014 and 1007 trials using the EuroQol-Five Dimensions (EQ-5D-3L[79]) questionnaire. (Table 15). EQ-5D data are used in the company's economic models for first-line and subsequent-line therapy with crizotinib. The ERG considers that patients in the crizotinib arm of the PROFILE 1014 and 1007 trials experienced a greater HRQoL benefit compared with patients treated with chemotherapy. However, the magnitude of the benefit is unknown, as the ERG has some concerns with HRQoL from both trials.

Table 15 Company summary of EQ-5D results for PROFILE 1014 and PROFILE 1007

PROFILE 1014	PROFILE 1007
Completion rates of all questions of the EQ-5D questionnaire from evaluable patients in PROFILE 1014 ranged from [redacted] for crizotinib (over the first 30 of a total of 50 cycles) and [redacted] for chemotherapy (over the maximum six cycles). All but eight patients in the crizotinib group ([redacted]) and seven patients in the chemotherapy group ([redacted]) from the intention-to-treat (ITT) population completed all questions of the EQ-5D questionnaire at baseline	Completion rates of all questions of the EQ-5D questionnaire ranged [redacted]
Whereas no statistically significant changes from baseline where observed in the chemotherapy group over six cycles, patients in the crizotinib group showed a significant improvement from baseline ([redacted]) in EQ-5D VAS general health status scores in cycles 3 to 16 and 18 to 21 In a mixed-model analysis, crizotinib was associated with a statistically significant greater improvement in EQ-5D VAS scores compared to chemotherapy ([redacted])	[redacted] Throughout the study, absolute EQ-5D index scores were [redacted] The difference between groups became [redacted] only found to be statistically significant for Cycles 6 and 7
In a mixed-model analysis the overall EQ-5D index score (utility) was found to be statistically significantly higher in the crizotinib group compared to chemotherapy ([redacted]); improvements from baseline in EQ-5D index scores were also statistically significantly greater in the crizotinib group relative to chemotherapy ([redacted]	Absolute EQ-5D index scores and the change from baseline in EQ-5D index scores for crizotinib compared to docetaxel are presented in Table 17. [redacted]
Statistically significant improvements from baseline ([redacted]) in EQ-5D index scores were observed in some cycles in the crizotinib group (Cycles 2 to 20, 22, 24, 25, 29 and 30), but were not observed in any cycles in the chemotherapy group (Cycles 1 to 6)	

EQ-5D= EuroQol-Five Dimensions; ITT=intention to treat; VAS=visual analogue scale
Source: CS, pp55-57

The company reports (CS, p65) that HRQoL data were collected during the PROFILE 1014 and 1007 trials using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC-QLQ-C30[80]) questionnaire and the EORTC QLQ-Lung Cancer LC13[81] module. The company has not reported the results from the EORTC questionnaires in the CS, but signposts the reader instead to the CS for TA406 and TA442.

The ERG notes that the company also collected data during the PROFILE 1014 and 1007 trials using the Visual Symptom Assessment Questionnaire (VSAQ-ALK) questionnaire. The questionnaire was designed to provide information about visual problems experienced by patients in the trials. The results of the questionnaire are not reported in the CS, but are reported in the CSRs for the trials.

The company claims (CS, p77) that the improvements in HRQoL seen in patients with ALK+ advanced NSCLC in untreated and previously treated settings are likely to be experienced by patients with ROS1+ advanced NSCLC. Clinical advice to the ERG is that HRQoL outcomes

of patients with ALK+ advanced NSCLC from the PROFILE 1014 and 1007 trials would be similar for patients with ROS1+ advanced NSCLC.

4.5 Adverse events

The company presents details of the AEs experienced by the 53 patients with ROS1+ advanced NSCLC who were recruited to the PROFILE 1001 study (CS, Section B.2.10). The ERG notes that the data from the PROFILE 1001 study are the only AE data available for patients with ROS1+ advanced NSCLC.

In support of the AE data from the PROFILE 1001 study, the company also presents details of the AEs experienced by patients with ALK+ advanced NSCLC who were treated with crizotinib in the PROFILE 1014 and 1007 trials and from patients in two single-arm studies i.e., PROFILE 1005[82] and PROFILE 1001[83] (ALK cohort).

PROFILE 1001 study

The company states (CS, p71) that the median treatment duration of crizotinib was 23.2 months (95% CI: 15.0 to NR) and, at data cut-off, 47.2% of patients remained on treatment. Treatment-emergent AEs reported during the PROFILE 1001 study are listed in Table 16. The company considers that crizotinib was well-tolerated due to the low numbers of patients who discontinued treatment due to AEs. The ERG notes that 98.1% patients experienced an AE considered to be treatment-related and 30.2% of patients experienced a Grade 3 or Grade 4 AE considered to be treatment-related.

Table 16 PROFILE 1001 Treatment-emergent AEs

Adverse event, No. of patients (%)	Crizotinib (N=53)	
	All cause n (%)	Treatment-related n (%)
Number of patients		
With AEs	53 (100)	52 (98.1)
With SAEs	22 (41.5)	2 (3.8)
With Grade 3 or 4 AEs	28 (52.8)	16 (30.2)
With Grade 5 AEs	9 (17.0)	0
With AEs associated with:		
Permanent discontinuation	4 (7.5)	1 (1.9)
Dose reduction	6 (11.3)	6 (11.3)
Temporary discontinuation	24 (45.3)	13 (24.5)

AE=adverse events; SAE=serious adverse event.
Source: CS, Table 18

The most frequently reported AEs (≥10%) in the PROFILE 1001 study are listed in Table 17. The most commonly occurring AE was vision disorder, experienced by almost 90% of patients.

The company reports (CS, p71) that treatment discontinuations and dose reductions were not associated with vision disorders. Other frequently reported AEs were nausea, oedema, vomiting, diarrhoea and constipation. The company reports (CS, p71) that most AEs were managed by either dose interruptions of dose reductions. One patient with nausea discontinued treatment.

Table 17 PROFILE 1001 Most frequently (≥10%) reported AEs

Adverse event	Crizotinib (N=53)	
	All cause n (%)	Treatment-related n (%)
Vision disorder	46 (86.8)	45 (84.9)
Nausea	31 (58.5)	26 (49.1)
Oedema	29 (54.7)	24 (45.3)
Vomiting	27 (50.9)	20 (37.7)
Diarrhoea	24 (45.3)	22 (41.5)
Constipation	23 (43.4)	18 (34.0)
Dizziness	21 (39.6)	10 (18.9)
Upper respiratory infection	21 (39.6)	0
Elevated aminotransferases	19 (35.8)	16 (30.2)
Fatigue	17 (32.1)	10 (18.9)
Neuropathy	16 (30.2)	5 (9.4)
Dyspnoea	15 (28.3)	1 (1.9)
Rash	14 (26.4)	7 (13.2)
Bradycardia	14 (26.4)	11 (20.8)
Decreased appetite	13 (24.5)	6 (11.3)
Headache	13 (24.5)	0
Abdominal pain	12 (22.6)	3 (5.7)
Dysgeusia	12 (22.6)	10 (18.9)
Cough[c]	11 (20.8)	0
Pyrexia	10 (18.9)	0
Disease progression	9 (17.0)	0
Hypophosphataemia	9 (17.0)	8 (15.1)
Neutropenia	9 (17.0)	7 (13.2)
Arthralgia	8 (15.1)	0
Pneumonia	8 (15.1)	0
Back pain	7 (13.2)	0
Pulmonary embolism	7 (13.2)	0
Pain in extremity	7 (13.2)	0
Pruritus	7 (13.2)	3 (5.7)
Blood creatinine increased	6 (11.3)	2 (3.8)
Chest pain	6 (11.3)	0
Dyspepsia	6 (11.3)	5 (9.4)
Fall	6 (11.3)	0
Stomatitis	6 (11.3)	1 (1.9)
Wheezing	6 (11.3)	0

Source: CS, Table 19

Grade 3 and 4 AEs (≥2%) from the PROFILE 1001 study are listed in Table 18. The company reports that, except for pulmonary embolism, all AEs were considered to be Grade 3.

Table 18 PROFILE 1001 Grade 3 and Grade 4 AEs (≥2%)

Adverse event	Crizotinib (N=53)	
	All cause n (%)	Treatment-related n (%)
Hypophosphatemia	8 (15.1)	7 (13.2)
Neutropenia	5 (9.4)	5 (9.4)
Headache	4 (7.5)	0
Dyspnoea	3 (5.7)	0
Syncope	3 (5.7)	0
Vomiting	3 (5.7)	1 (1.9)
Electrocardiogram QT prolonged	2 (3.8)	1 (1.9)
Elevated transaminases	2 (3.8)	2 (3.8)
Pneumonia	2 (3.8)	0
Pulmonary embolism	6 (11.3)	0

Source: CS, Table 19

The company states (CS, p74) that 16 patients in the PROFILE 1001 study died due to progressive disease, 9 deaths occurred within 28 days of the last treatment and 7 deaths occurred more than 28 days since their last treatment. One patient died from unknown causes 8 months after their last treatment.

Supporting evidence from trials and studies in patients with ALK+ advanced NSCLC

The company reports the results of a pooled analysis of AE data from four sources of clinical evidence, the PROFILE 1014 and 1007 trials and the PROFILE 1005[82] and 1001[83] (ALK+ cohort) studies. The company states that the results of the pooled analysis are described in the EPAR[84,85] for crizotinib.

The company compares the baseline characteristics of the 53 patients with ROS1+ advanced NSCLC from the PROFILE 1001 study with the characteristics of the 1669 patients with ALK+ advanced NSCLC who are included in the pooled safety analysis (CS, Table 23). The company states that the two patient populations have similar baseline characteristics; however, the ERG notes from Table 23 of the CS that the 53 patients with ROS1+advanced NSCLC are slightly younger than the 1669 patients with ALK+ advanced NSCLC and that the smoking status of the patients with ALK+ advanced NSCLC is not available for comparison.

The company compares the AEs (any grade and Grades 3 or 4) experienced by the 53 patients with ROS1+ advanced NSCLC from the PROFILE 1001 study with the AEs (any grade and Grades 3 or 4) experienced by the 1669 patients with ALK+ advanced NSCLC who are included in the pooled safety analysis (CS, Table 24). The ERG agrees with the company that

the types and frequency of AEs are similar between patients with ROS1+ advanced NSCLC (PROFILE 1001) and patients with ALK+ advanced NSCLC who were treated with crizotinib.

Summary of AE evidence

The most frequently occurring AE of any grade experienced by the 53 patients in the PROFILE 1001 study was 'vision disorder'. The company reports that vision disorders were Grade 1 or Grade 2 and were managed with dose reductions. The company also reports that other common AEs (e.g. nausea, vomiting) were also Grade 1 or Grade 2 events that were managed with dose interruptions or reductions. The most frequently experienced Grade 3 AEs were hypophosphataemia and neutropenia. The only Grade 4 AEs recorded during the PROFILE 1001 study were six cases of pulmonary embolism. These were not considered by the company to be treatment-related. The ERG notes that the AE data from the PROFILE 1001 study are the only AE data that are available for a patient population with ROS1+ advanced NSCLC.

The company states (CS, p77) that the AE profile of crizotinib as recorded in the PROFILE 1001 study is consistent with the AE profile of crizotinib as reported in the pooled analysis of 1669 patients with ALK+ advanced NSCLC. The ERG notes that the EMA[14] (EPAR, p60) considered the safety profile of crizotinib in the 53 patients with ROS1+ advanced NSCLC to be consistent with the known safety profile of crizotinib.

4.6 Results of other studies identified in the clinical systematic review

In this section, the ERG summarises the key findings from two studies identified by the company as being relevant to a ROS1+ UK population and discusses whether data from these studies support the use of crizotinib in ROS1+ patients. The company summarises the results of the other 13 studies identified in the clinical systematic review in Appendix D of the CS (Table 8). None of these studies were used to provide estimates of clinical or cost effectiveness in the CS, as discussed in Section 4.2.1.

The EUCROSS study (n=34) is a phase II single-arm study conducted in a European ROS1+ NSCLC population. The company presents preliminary results from this recently completed study as supportive evidence for the clinical effectiveness of treatment with crizotinib. The ORR from EUCROSS ([redacted]) was very similar to the ORR reported in the PROFILE 1001 study. Median PFS ([redacted] months, 95% CI: [redacted]) and the probability of survival at 12 months ([redacted]) in the EUCROSS study were also comparable to the corresponding results from the PROFILE 1001 study. The probability of survival at 24 months in the EUCROSS study was [redacted]). The company claims that, as results from EUCROSS support the observations from the PROFILE 1001

study, the results from ROS1 patients in the PROFILE 1001 study may be generalisable to the UK population. The ERG agrees that the EUCROSS study results suggest that the PROFILE 1001 study results are generalisable to the UK population. The company states that because of the lack of K-M curves for PFS and OS from the EUCROSS study at the time of the economic analysis, evidence from the EUCROSS study could not be incorporated in the economic analysis.

The company also refers to the recent audit of ROS1 patients from the [redacted], UK, explaining that this audit provides supportive data for the use of crizotinib in ROS1+ advanced NSCLC patients. The preliminary results from the [redacted] audit were presented to the company by the lead investigator [redacted] during an advisory board meeting[22] in July 2017. This audit identified [redacted] patients with ROS1+ NSCLC in the UK, of whom [redacted] received first-line pemetrexed+platinum and [redacted] received first-line and subsequent-line crizotinib. [redacted] The preliminary median PFS was [redacted] months for patients treated by pemetrexed+platinum and maintenance pemetrexed in the first-line setting, and [redacted] months for treatment with crizotinib in the first-line and subsequent-line settings. The median PFS observed for crizotinib-treated patients from the audit is lower than the median PFS for patients receiving crizotinib in the PROFILE 1001 study. The company states that at the advisory board meeting[22] where the audit data were reviewed, the difference in the PFS data between the [redacted] audit and the PFS data from the PROFILE 1001 study was "…felt to be due to the real-world nature of the audit of UK patients". Median OS [redacted] The survival rate at Year 1 is comparable to the 12-month survival rate for patients in the PROFILE 1001 study.

4.7 Critique of the company's approach to obtaining estimates of the clinical effectiveness of crizotinib in the ROS1+ patient population

The company presents evidence for the effectiveness of crizotinib in comparison to chemotherapy from the PROFILE 1014 and PROFILE 1007 trials, which were conducted in the ALK+ advanced NSCLC patient population, as a proxy for evidence for the effectiveness of crizotinib in comparison to chemotherapy in the ROS1+ advanced NSCLC patient population. The company's justification for this approach with regards to the similarity of the two patient populations is discussed in Section 2.1 of this ERG report. In this section, the ERG outlines and critiques the company's statistical rationale for this approach.

The company considered performing unanchored matched adjusted indirect comparisons (MAIC) to compare crizotinib treated ROS1+ patients in the PROFILE 1001 study with the chemotherapy arm of the PROFILE 1014 trial and with the chemotherapy arm of the PROFILE 1007 trial in separate analyses. The company refers to the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 which recommends that an unanchored MAIC should adjust for all effect modifiers and prognostic variables. The company considered it implausible to fit complex models including multiple variables given the small sample size in the PROFILE 1001 study. The ERG agrees with the company's assessment.

The company explains (CS, p68) that "…given the structural similarities between the ALK and ROS1 rearrangements and the comparable patient characteristics between ALK+ and ROS1+ NSCLC patients, it was preferable to use HRs from the PROFILE 1014 and PROFILE 1007 trials rather than attempting to implement complex methods with only limited data". However, the ERG notes that the CIs for the estimates of median PFS do not overlap, so median PFS is statistically significantly longer for ROS1+ NSCLC patients treated with crizotinib in the PROFILE 1001 study than for ALK+ NSCLC patients treated with crizotinib in the PROFILE 1014 and PROFILE 1007 trials. The 95% CI for median PFS for the PROFILE 1001 study takes into consideration the small sample size of the study. The difference between PFS in the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials causes the ERG to question whether the ALK+ and ROS1+ NSCLC patient populations are truly comparable.

In the company's response to the ERG's clarification letter, the company suggests that selection bias in the PROFILE 1001 study could be to blame for the differences in PFS results between the PROFILE 1001 study and the PROFILE 1014 and PROFILE 1007 trials. However, the ERG notes that, in the CS, it is stated that "UK clinical experts confirmed that the baseline characteristics in the PROFILE 1001 study are representative of patients encountered in UK clinical practice, and as such selection bias is unlikely to be a concern".

The company also states that real-world evidence from the [redacted] shows PFS outcomes for UK crizotinib-treated ROS1+ NSCLC patients to be in line with the PFS results seen in the ALK+ NSCLC trials. However, if the differences between the [redacted] PFS results and the PROFILE 1001 study PFS results are considered to be due to the "real-world" nature of the data as explained by the company, the ERG is unsure why the company believes that it is appropriate to compare data from the [redacted] with data from the RCTs to demonstrate that PFS results are similar for ROS1+ and ALK+ advanced NSCLC patient populations.

Finally, the company states that, if there were differences in the PFS for ROS1+ and ALK+ NSCLC patients treated with crizotinib, then the results of the PROFILE 1001 study would indicate that the ALK data provide a conservative estimate of the clinical benefits of crizotinib in patients with ROS1+ advanced NSCLC. The ERG agrees that this is the case, but highlights that, since patients are treated until progression, underestimating PFS (and consequently the time on treatment) would have important implications for the cost effectiveness of crizotinib.

4.8 Conclusions of the clinical effectiveness section

The ERG considers that the company has addressed the decision problem **only** if the outcomes from patients with ALK+ advanced NSCLC can be used as a proxy for the outcomes of patients with ROS1+ advanced NSCLC.

Direct clinical evidence (PROFILE 1001)

The direct clinical effectiveness evidence for crizotinib in the treatment of patients with ROS1+ advanced NSCLC was derived from the PROFILE 1001 study. The ERG highlights the following points:

- The PROFILE 1001 study is a small, single-arm phase I study (n=53). Patients recruited to the study were previously untreated (n=7) or had received one or more previous treatments. Of the previously treated patients, 63% had not received treatment with pemetrexed+platinum at first-line. Pemetrexed+platinum is the standard of care in the UK as a first-line treatment for patients with tumours of adenocarcinoma histology

- ROS1+ NSCLC (PROFILE 1001) and ALK+ NSCLC (PROFILE 1014 and PROFILE 1007) patient populations are broadly comparable in terms of baseline characteristics

- The ERG considers that the PROFILE 1001 study was well designed and conducted and included an independent review of radiological outcomes

- In the PROFILE 1001 study, most of the patients achieved either a partial or complete response with crizotinib (69.8%), and median PFS was 19.3 months (95% CI: 14.8 to not reported [NR]). OS data were immature, with only 30% of patients having died at the latest data cut-off date (2014)

- No HRQoL data were collected during the PROFILE 1001 study

- There are no robust OS data available for patients with ROS1+ advanced NSCLC

Proxy clinical evidence (PROFILE 1014, PROFILE 1007)

The company presents data from the PROFILE 1014 and PROFILE 1007 RCTs, which investigated the efficacy of first-line (PROFILE 1014) and subsequent-line (PROFILE 1007) crizotinib in comparison to chemotherapy in ALK+ advanced NSCLC patients, as supportive evidence for the use of crizotinib in patients with ROS1+ advanced NSCLC. The ERG highlights the following points:

- The ERG considers that the PROFILE 1014 and 1007 trials well generally well designed and conducted
- In the PROFILE 1007 trial, [redacted] of patients were not treated with pemetrexed+platinum in the first-line setting. Pemetrexed+platinum is the standard of care in the UK as a first-line treatment for patients with tumours of adenocarcinoma histology
- None of the patients in the PROFILE 1007 were treated with docetaxel+nintedanib (NHS standard care)
- Patients in the PROFILE 1014 trial were considered by a previous Appraisal Committee not be representative of patients likely to be treated with crizotinib in the NHS. However, clinical advice to the ERG is that patients in the PROFILE 1001 study and patients in the PROFILE 1014 and 1007 trials have similar baseline characteristics and broadly represent patients likely to be treated in the NHS
- The ERG concluded that the PH assumption was not valid for PFS in the PROFILE 1014 or PROFILE 1007 trials, and that HRs for PFS data from both trials should be interpreted with caution
- The ORRs for crizotinib patients in the PROFILE 1014 (74.4%) and PROFILE 1007 (65.3%) trials were comparable with the observed ORR for patients in the PROFILE 1001 study. Both the PROFILE 1014 and PROFILE 1007 trials demonstrated a statistically significantly greater ORR for crizotinib patients than for chemotherapy patients
- Median PFS varied across the PROFILE 1001 study (19.3 months, 95% CI: 14.8 to NR), the PROFILE 1014 trial (10.9 months, 95% CI: 8.3 to 13.9) and the PROFILE 1007 trial (7.7 months, 95% CI: 6.0 to 8.8; respectively). The variation in PFS brings into question the comparability of the ALK+ and ROS1+ NSCLC patient populations

- There was a substantial amount of patient crossover from the chemotherapy arm to the crizotinib arm and vice versa in both the PROFILE 1014 and PROFILE 1007 trials
- The company presents RPSFTM-adjusted OS HRs to account for patient crossover in the PROFILE 1014 trial. The ERG considers that the RPSFTM-adjusted HRs for OS are unlikely to be valid and should be interpreted with caution
- For the PROFILE 1007 trial, the company presents the PFS HR as a proxy for the true OS HR, instead of using the RPSFTM-adjusted OS HR. The ERG considers that the PFS HR is likely to be closer to the true OS HR than the RPSFTM-adjusted OS HR. However, the ERG also notes that the true OS HR may still be less than the PFS HR, and the company's HR for "crossover-adjusted" OS should be interpreted with caution
- There are no reliable OS data available from either the PROFILE 1014 or PROFILE 1007 trials to support treatment with crizotinib

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company in support of the use of crizotinib for the treatment of patients with ROS1+ advanced NSCLC. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluations. The company has also provided an electronic version of their economic models, which were developed in Microsoft Excel.

5.2 ERG comment on company's review of cost effectiveness evidence

5.2.1 Objective of cost effectiveness review

The company conducted a systematic review of published cost effectiveness studies relevant to the decision problem on 17 March 2017. The company states that they searched the following databases: MEDLINE, MEDLINE in Process, EMBASE, The Cochrane Library (NHS Economic Evaluation Database [NHS-EED; Issue 2 of 4, April 2015] and Health Technology Assessment Database [Issue 4 of 4, October 2016]) and EconLit. The search strategy included relevant disease terms and a cost effectiveness filter. Details of the search strategies employed by the company are provided in Appendix G of the CS. Electronic database searches were supplemented by additional hand searches of proceedings from the ASCO, ELCC, ESMO, ISPOR and WCLC meetings on 1st June 2017. The company states that the searches of conference proceedings were limited to those published between 2015 and 2017. The company assumed that older, pre-2015 conference abstracts would have since been published as full-text articles in peer reviewed journals. NICE and Scottish Medicines Consortium (SMC) websites were searched on 1st December 2016 for economic evaluations presented in relevant health technology assessment appraisals.

The company conducted additional systematic reviews to identify HRQoL studies and cost and healthcare resource identification studies using the search results from a previous STA submission to NICE (TA406). The searches were updated from 31st July 2015 up to 17th March 2017. The ERG considers the approach to update the previous searches to be appropriate.

5.2.2 Eligibility criteria used in study selection

The eligibility criteria used by the company to facilitate study selection are described in Table 23, Appendix G of the CS. The ERG considers that the eligibility criteria were appropriate to the objective of the company's review of cost effectiveness evidence.

5.2.3 Included and excluded studies

The company did not identify any cost effectiveness studies that were relevant to the ROS1+ advanced NSCLC population.

5.3 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and considers that the databases searched and search terms used appear to be reasonable. The ERG updated the company searches for the period between March 2017 and 9th November 2017 and is satisfied that no relevant economic studies have been missed by the company.

5.4 Summary and critique of company's submitted economic evaluation by the ERG

5.4.1 Model structure

The company developed a de novo cost effectiveness model structure in Microsoft Excel. The same model structure is used for the analysis of first- and subsequent-line treatment with crizotinib, but considering different comparator, cost, efficacy and benefit inputs applied to each population. The model comprises three progressively worse health states: progression-free disease, progressed disease and death (Figure 2). All patients begin in the model in the progression-free state and are at risk of moving to a worse state in each subsequent cycle, where death is an absorbing health state.

The company uses a 30-day cycle length and has implemented a half-cycle correction. This model structure was used in the appraisal of crizotinib for untreated and previously treated patients with ALK+ advanced NSCLC (NICE TA406[36] and TA422[60]).

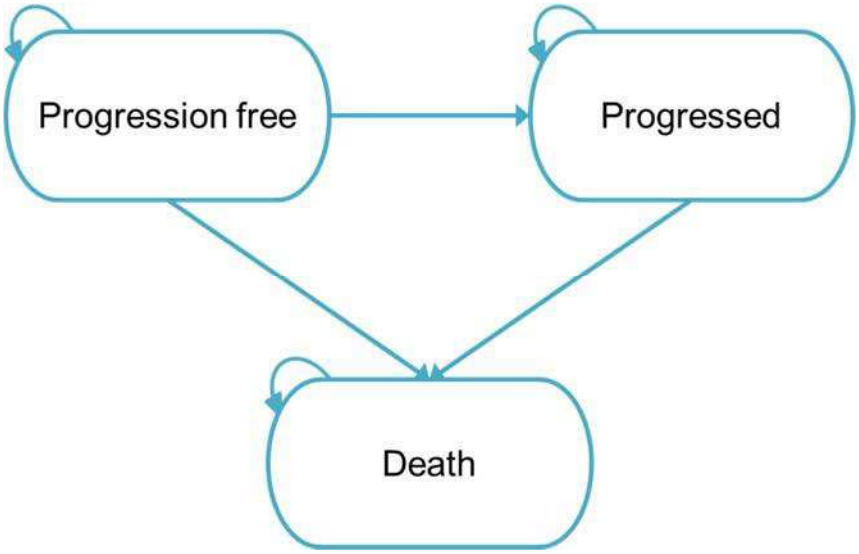


Figure 2 Company model structure

Source: CS, Figure 9

5.4.2 Population

The population reflected in the model is adults with ROS1+ advanced NSCLC. This is split into two populations to encompass first- and subsequent-line treatment with crizotinib. Due to the limited availability of time-to-event data for patients with ROS1+ advanced NSCLC, the company has used data from the ALK+ advanced NSCLC population as a proxy for data fromROS1+ patients in the base case analysis.

5.4.3 Interventions and comparators

Intervention

Crizotinib is supplied as a capsule and is used to treat patients in line with its EMA marketing authorisations (i.e. 250 mg twice daily until disease progression). Treatment beyond progression was allowed in the pivotal studies (PROFILE 1001 study, PROFILE 1014 trial and PROFILE 1007 trial), which is reflected in the company's model.

Comparators (first-line treatment)

Pemetrexed+platinum therapy (cisplatin or carboplatin) is the only comparator included in the cost effectiveness analysis for first-line treatment. The dose of pemetrexed is 500 mg/m², followed by cisplatin (75 mg/m²) or carboplatin (target area under the concentration-time curve of 5-6 mg/mL/min) administered intravenously on the first day of each 21-day cycle.[36] Treatment is administered in the base case model based on the time on treatment curves from TA406.

Comparators (subsequent-line treatment)

Docetaxel monotherapy is the only comparator included in the cost effectiveness analysis for subsequent-line treatment; however, evidence for docetaxel monotherapy used in the subsequent-line model is based on the pooled outcomes of patients treated with either docetaxel monotherapy or pemetrexed+platinum ('pooled chemotherapy') in the PROFILE 1007 trial. The company cites paucity of data in either the ROS1+ or ALK+ advanced NSCLC population for the omission of a comparison with docetaxel+nintedanib or with BSC. Docetaxel is administered intravenously at a dose of 75 mg/m^2 every 21 days. Treatment is administered in the base case model for a maximum of three cycles.

Subsequent treatment (first-line treatment)

Patients who progress after first-line treatment with crizotinib or pemetrexed+platinum therapy (and are no longer receiving treatment with crizotinib or pemetrexed+platinum therapy) are treated with docetaxel or receive BSC.

Subsequent treatment (subsequent-line treatment)

Patients who progress after subsequent-line treatment after receiving treatment with crizotinib or docetaxel receive BSC.

5.4.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services (PSS) and the model time horizon is 20 years. The company states that both costs and benefits are discounted at a rate of 3.5% per annum.

5.4.5 Treatment effectiveness and extrapolation

The company has used clinical effectiveness data from patients with ALK+ advanced NSCLC as a proxy for data from patients with ROS1+ advanced NSCLC in the base case analysis for both first-line and subsequent-line treatment with crizotinib (the company's rationale for this approach and further details are presented in Sections 2.1, 3.1-3.3 of this ERG report).

For the first-line population, extrapolations of PFS and time to treatment discontinuation (TTD) data for patients with ALK+ advanced NSCLC were taken from TA406 (based on the results of the PROFILE 1014 trial). The company has updated its modelling of OS since TA406 and has provided new results based on an updated data cut (9 March 2017) from the PROFILE 1014 trial.

For the subsequent-line population, extrapolations of OS, PFS and TTD data for patients with ALK+ advanced NSCLC were taken from TA422 (based on the results of the PROFILE 1007 trial).

The company has provided a scenario analysis using clinical effectiveness data for patients with ROS1+ advanced NSCLC from the PROFILE 1001 study.

A summary of all time-to-event modelling is presented in Table 19.

Table 19 Time-to-event modelling in company base case and scenario analysis

		Base case		Scenario	
		First-line (ALK+, PROFILE 1014)	**Subsequent-line (ALK+, PROFILE 1007)**	**First-line (ROS1+, PROFILE 1001)**	**Subsequent-line (ROS1+, PROFILE 1001)**
OS	**Crizotinib**	Exponential (independent) adjusted for: • RPSFTM [Wilcoxon] • patient characteristics	Exponential (PH) adjusted from comparator HR=0.49 (CI=0.37 to 0.64)	Exponential (PH)	Same as first-line
	Comparator	Exponential (independent) adjusted for: • RPSFTM [Wilcoxon] • patient characteristics	Exponential (PH) Adjusted for: • RPSFTM [log rank]	Exponential (PH) adjusted from intervention HR=[redacted]	Exponential (PH) adjusted from intervention HR=[redacted]
PFS	**Crizotinib**	Stratified log-normal adjusted for: • patient characteristics	Weibull	Exponential (PH)	Same as first-line
	Comparator	Stratified generalised gamma adjusted for: • patient characteristics	Log-normal	Exponential (PH) adjusted from intervention HR=[redacted]	Exponential (PH) adjusted from intervention HR=[redacted]
TTD	**Crizotinib**	Stratified exponential (independent) adjusted for: • patient characteristics	Weibull	Exponential	Same as first-line
	Comparator	Stratified gompertz (independent) adjusted for: • patient characteristics	3 cycles only	Stratified gompertz (independent) adjusted for: • patient characteristics	3 cycles only

HR=hazard ratio; PFS=progression-free survival; OS=overall survival; PH=proportional hazard; RPSFTM=rank-preserving structural failure time method; TTD=time to treatment discontinuation
Source: CS, company model

Base case: first-line treatment

Overall survival

Data from the PROFILE 1014 trial (data cut-off: March 09, 2017) were used as the basis for identifying parametric models to represent OS for patients treated with first-line treatments. The RPSFTM (Wilcoxon) method was used in the base case analysis to adjust OS for the effect of patients in the pemetrexed arm who crossed over to treatment with crizotinib on progression (n=144 [84.2%] of patients who had progressed at the time of the final OS analysis).

Parametric curves were fitted separately to the RPSFTM-adjusted for treatment with crizotinib and for treatment with pemetrexed+platinum therapy. The parametric models considered were: exponential, weibull, log-normal, log-logistic, gompertz and generalised gamma. Model fit was assessed using visual inspection, comparison of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), and consideration of the clinical plausibility of long-term extrapolation results. The exponential curve was selected in the base case analysis for the intervention and the comparator treatments. Alternative curve fits are tested in the sensitivity analysis.

As discussed in TA406, the baseline characteristics of patients participating in a 'real-life' cohort study conducted by Davis[76] were considered to be more representative of the characteristics of patients likely to be seen in NHS clinical practice than those of patients in the PROFILE 1014 trial. In TA406, the company adjusted the PFS and OS data from the PROFILE 1014 trial to account for the baseline characteristics of the patients in the Davis[76] study (Table 20). For the current appraisal, the company has adjusted the chosen exponential OS curves to take account of the baseline patient characteristics reported by Davis[76] to provide consistency with the PFS and TTD modelling from TA406.

Table 20 Baseline demographics and patient characteristics for covariate-adjustment

Covariate	Real-world data (Davis[76])	Crizotinib (PROFILE 1014)	Pemetrexed+platinum therapy (PROFILE 1014)	Pooled treatments (PROFILE 1014)
% non-Asian	87.6%	55.2%	53.2%	54.2%
% age ≥ 65	29.2%	13.4%	18.7%	16.0%
% male	67.9%	39.5%	36.8%	38.2%
% smoker or ex-smoker	62.8%	38.4%	34.5%	36.4%
% ECOG PS 0-1	78.1%	94.2%	95.3%	94.7%
% ECOG PS 2	21.9%*	5.8%	4.7%	5.3%
% with brain metastases	NR	26.2%	27.5%	26.8%
% non-adenocarcinoma	NR	6.4%	5.8%	6.1%

ECOG=Eastern Cooperative Oncology Group; NR=not reported; PS=performance status
Source: CS, Table 29

The OS curves used in the company's first-line base case analysis are shown in Figure 3. Mean OS in the company's first-line base case model is 46.4 months for treatment with crizotinib and 17.6 months for treatment with pemetrexed+platinum, which yields an OS gain of 28.7 months.

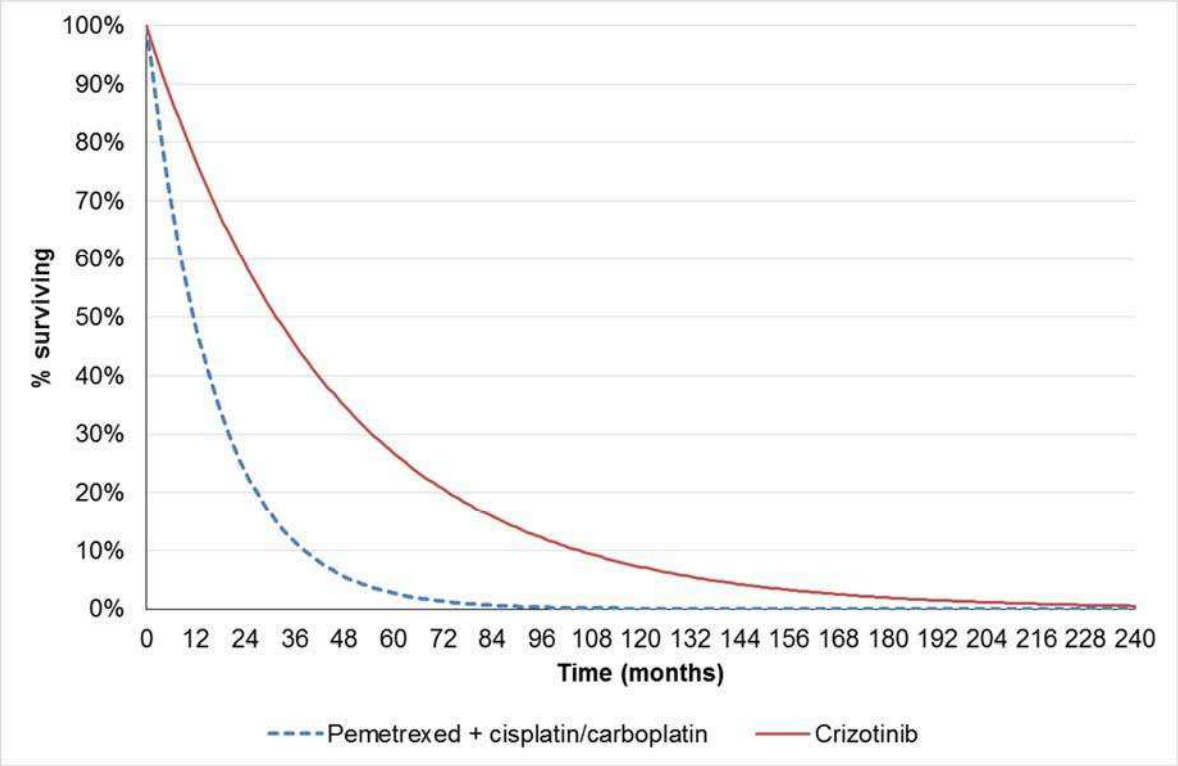


Figure 3 Company model first-line base case OS

Source: company model

Progression-free survival

Data from the PROFILE 1014 trial (data cut-off: 30 November 2013) were used as the basis for identifying parametric models to represent PFS in the first-line setting. Fully stratified log-normal curve is used to estimate PFS for treatment with crizotinib and a fully stratified gamma curve is used to estimate PFS for treatment with pemetrexed+platinum in the first-line setting for this appraisal; the curves have been adjusted according to the baseline characteristics of the patients in the Davis study.[76]

The company states that the PFS curves used in the company model replicate directly those accepted by the Appraisal Committee during TA406. No additional rationale was provided for the choice of PFS curves in the current CS. The ERG notes that it is not clear from the Final Appraisal Determination document for TA406 that the curves used in the company's base case were in fact accepted by the Appraisal Committee, only that the ERG's alternative analyses were not considered to be plausible.

The PFS curves used in the company's first-line base case analysis are shown in Figure 4. Mean PFS in the company's first-line base case model is 16.8 months for treatment with crizotinib and 7.3 months for treatment with pemetrexed+platinum, which yields a PFS gain of 9.5 months.

Figure 4 Company model first-line base case PFS

Source: company model

Time to treatment discontinuation

The company states that the TTD curves used in the company model replicate directly those accepted by the Appraisal Committee during TA406. Data from the PROFILE 1014 trial (data cut-off: November 30, 2013) were used as the basis for identifying parametric models to represent TTD in the first-line setting for treatment with crizotinib and with pemetrexed+platinum therapy in TA406. A fully stratified (independent) exponential curve is used to estimate TTD for treatment with crizotinib and a fully stratified gompertz curve is used to estimate TTD for treatment with pemetrexed+platinum in the first-line setting for this appraisal, which have been adjusted to take account of the baseline characteristics of the patients in the Davis study.[76]

The company has not presented any further information regarding the development of TTD estimates in this CS. The development of the TTD curves is outlined in the Appraisal Committee papers for TA406; however, much of the detail has been redacted and cannot be examined by the ERG.

Mean TTD in the company first-line base case model is 17.7 months for treatment with crizotinib and 3.8 months for treatment with pemetrexed+platinum.

Base case: subsequent-line treatment

Overall survival

The OS curves used in the company model replicate directly those accepted by the Appraisal Committee during TA422 and the company has not given any further information about their development in the current CS.

Data from the PROFILE 1007 trial were used as the basis for identifying a parametric model to represent OS in the subsequent-line setting in TA422. The Appraisal Committee's most plausible ICER per QALY gained for treatment with crizotinib versus docetaxel in TA422 included estimates of OS based on an exponential PH model using a HR of 0.49 (Section 4) and the company has replicated this approach in its subsequent-line model.

The OS curves used in the company's subsequent-line base case analysis are shown in Figure 5. Mean OS in the company subsequent-line base case model is 33.0 months for treatment with crizotinib and 16.7 months for treatment with docetaxel, which yields an OS gain of 16.3 months.

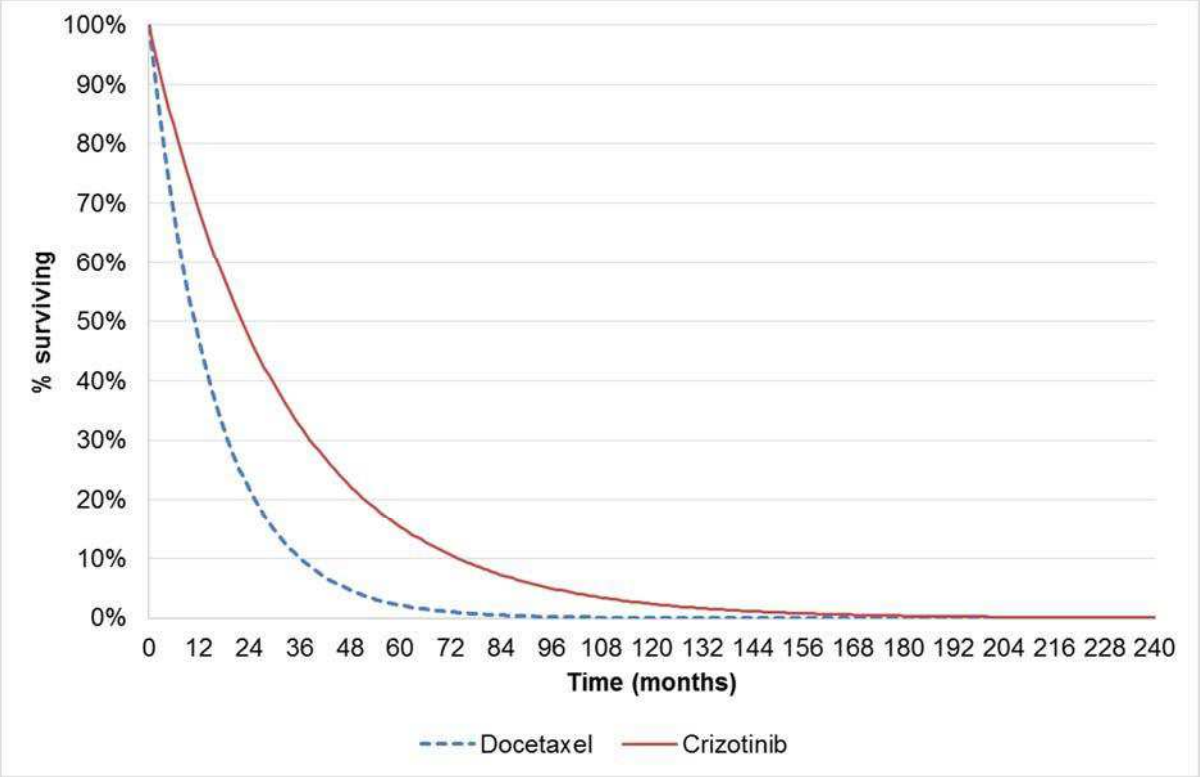


Figure 5 Company model subsequent-line base case OS

Source: company model

Progression-free survival

The company states that the PFS curves used in the company model for subsequent-line treatment replicate directly those accepted by the Appraisal Committee during TA422. Data from the PROFILE 1007 trial were used as the basis for identifying parametric models to represent PFS in TA422. The company used weibull and log-normal curves to model PFS in the subsequent-line setting for crizotinib and docetaxel respectively.

In TA296, the modelling of PFS was not an issue for consideration during the appraisal. TA296 was then superseded by TA422. As the modelling of PFS had not been an issue in TA296, there was no detailed description of the PFS model used in TA422. The company did not provide any further information to explain how the previously used PFS models were developed in the original submission for this appraisal. The company provided justification for the choice of modelling approaches at a late stage in the STA process.

The PFS curves used in the company's subsequent-line base case analysis are shown in Figure 6. Mean PFS in the company's subsequent-line base case model is 10.6 months for treatment with crizotinib and 4.9 months for treatment with docetaxel, which yields a PFS gain of 5.7 months.

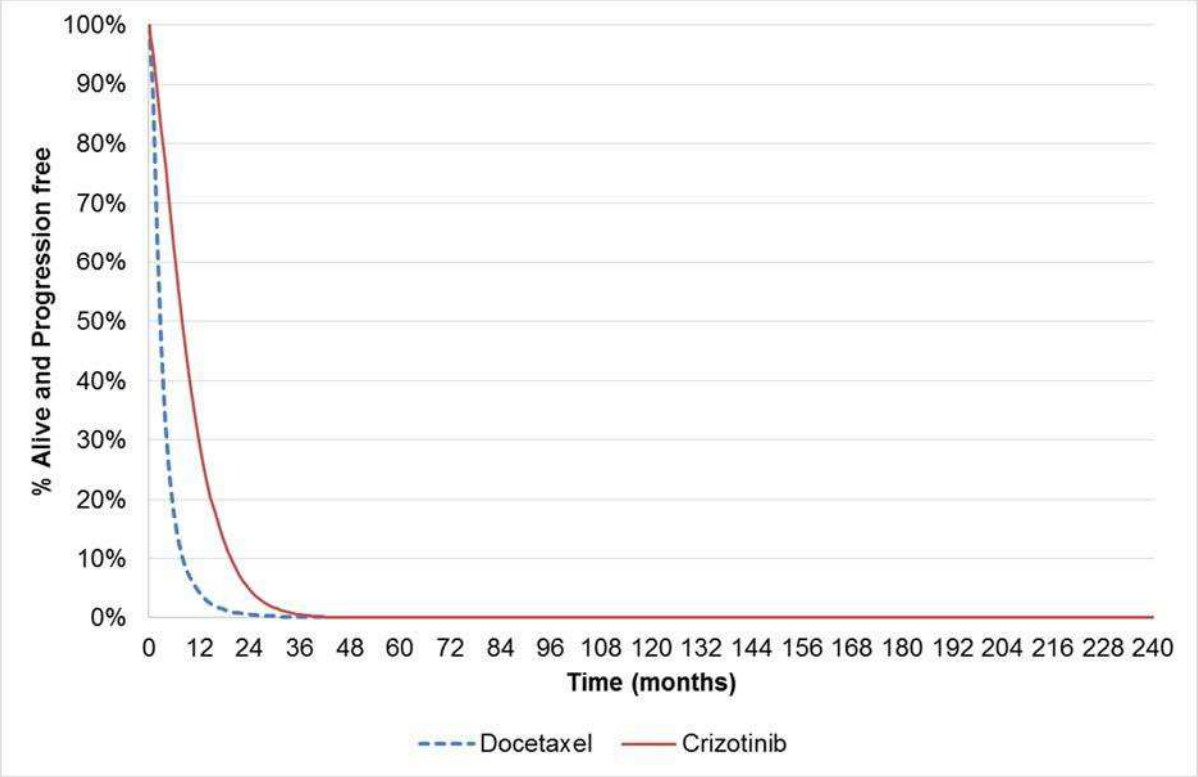


Figure 6 Company model subsequent-line base case PFS

Source: company model

Time to treatment discontinuation

The company states that the TTD curve used in the company's model for subsequent-line treatment with crizotinib replicate directly the model accepted by the Appraisal Committee during TA422. TTD was not modelled for treatment with docetaxel in TA422. Instead, a maximum of three doses was assumed for docetaxel and this is repeated in the current model. Data from the PROFILE 1007 trial were used as the basis for identifying a parametric model to represent TTD in TA422. The company used weibull curves to model TTD in the subsequent-line setting for treatment with crizotinib.

The ERG notes that the TTD curve was also used in TA296 (which was superseded by TA422). The modelling of TTD was an issue for consideration in TA422, as the company had updated the base case analysis from TA296. The Appraisal Committee did not accept the company's updated modelling of TTD and preferred the original base case analysis from TA296. In the current CS, the company did not originally provide any further information to explain how the previously used TTD models were developed. The company provided further information on model development at a late stage in the STA process.

Mean TTD in the company subsequent-line base case model is 15.5 months for treatment with crizotinib and 1.9 months (maximum 3 cycles) for treatment with docetaxel.

Scenario analysis

Time-to-event modelling (crizotinib)

The company used data from the single-arm PROFILE 1001 study to estimate OS, PFS and TTD for treatment with crizotinib in the ROS1+ advanced NSCLC population in a scenario analysis. Given the limited number of patients (n=7) and events (OS, n=2; PFS, n=3; TTD, n=4) for patients treated with crizotinib as a first-line treatment in the PROFILE 1001 study, the company considered it more robust to model all treatment lines together. The company notes that the majority of patients (n=46, 87%) in the PROFILE 1001 study received crizotinib as a subsequent-line treatment and that these patients therefore drive survival estimates for the overall population. The company considers this approach to be conservative, as it states that treatment-naïve patients would be expected to have greater survival estimates than previously treated patients.

The company states that, although the 'all-lines' approach to modelling data from the PROFILE 1001 study is less uncertain than modelling first- and subsequent-line treatments separately, there is still a lot of uncertainty due to the small sample size (n=53) and the immaturity of the data (30% of patients had died by data cut-off).

For each time-to-event outcome, the company fitted standard parametric curves to the K-M data for treatment with crizotinib from the PROFILE 1001 study and assessed the curves using visual inspection, consideration of the AIC and BIC, and the clinical plausibility of the results. The company notes in each case that there was little difference in the AIC and BIC for any of the curves. Exponential curves were chosen for OS, PFS and TTD based on clinical plausibility and marginally better statistical fit. Alternative distributions are considered in a scenario analysis.

The company has used the same 'all-lines' curves to estimate outcomes for first- and subsequent-line treatment with crizotinib. It then applied different HRs to OS, PFS and TTD for treatment with crizotinib to generate estimates of the outcomes for the first- and subsequent-line comparators.

Overall survival (comparators)

The company estimated OS for treatment with pemetrexed+platinum therapy in the first-line setting using the inverse of the crossover-adjusted HR from the updated PROFILE 1014 trial OS analysis (HR=[redacted]_applied to the chosen exponential curve for treatment with crizotinib. The RPSFT (Wilcoxon) method of crossover adjustment was preferred as it produced a conservative HR (Table 21).

Table 21 OS HRs from PROFILE 1014 used in the PROFILE 1001 scenario analysis (first-line setting)

	Crossover method	
	RPSFTM – Wilcoxon	**RPSFTM – log-rank**
HR (95% CI)	[redacted]	[redacted]
Inverse HR applied to the crizotinib OS curve (95% CI)	[redacted]	[redacted]

HR=hazard ratio; RPSFTM=rank preserving structural failure time method
Source: CS, Table 33

The company used the inverse of the crossover-adjusted HR from the pooled chemotherapy arm of the PROFILE 1007 trial (HR=2.61, CI: 1.01 to 23.81) to estimate OS for treatment with docetaxel in the subsequent-line setting. The company explains that the crossover-adjusted HR was not available for the docetaxel subgroup from the PROFILE 1007 trial and states that the HR from the pooled chemotherapy arm is a conservative assumption. The RPSFT (log-rank) method of crossover adjustment was preferred by the company as it was used in TA422 (Table 22).

Table 22 OS HRs from PROFILE 1007 used in the PROFILE 1001 scenario analysis (subsequent-line setting)

	Crossover method	
	RPSFTM – log-rank (base case)	**RPSFTM – Wilcoxon**
HR (95% CI)	0.38 (0.04 to 0.99)	0.40 (0.07 to 0.97)
Inverse HR applied to the crizotinib OS curve (95% CI)	2.61 (1.01 to 23.81)	2.49 (1.03 to 14.49)

HR=hazard ratio; RPSFTM=rank preserving structural failure time method
Source: CS, Table 34

The final OS curves used in the company's first-line PROFILE 1001 scenario analysis are shown in

Figure 7. Mean OS in the company's first-line PROFILE 1001 scenario analysis model is 69.0 months for treatment with crizotinib and 25.8 months for treatment with pemetrexed+platinum, which yields an OS gain of 43.2 months.

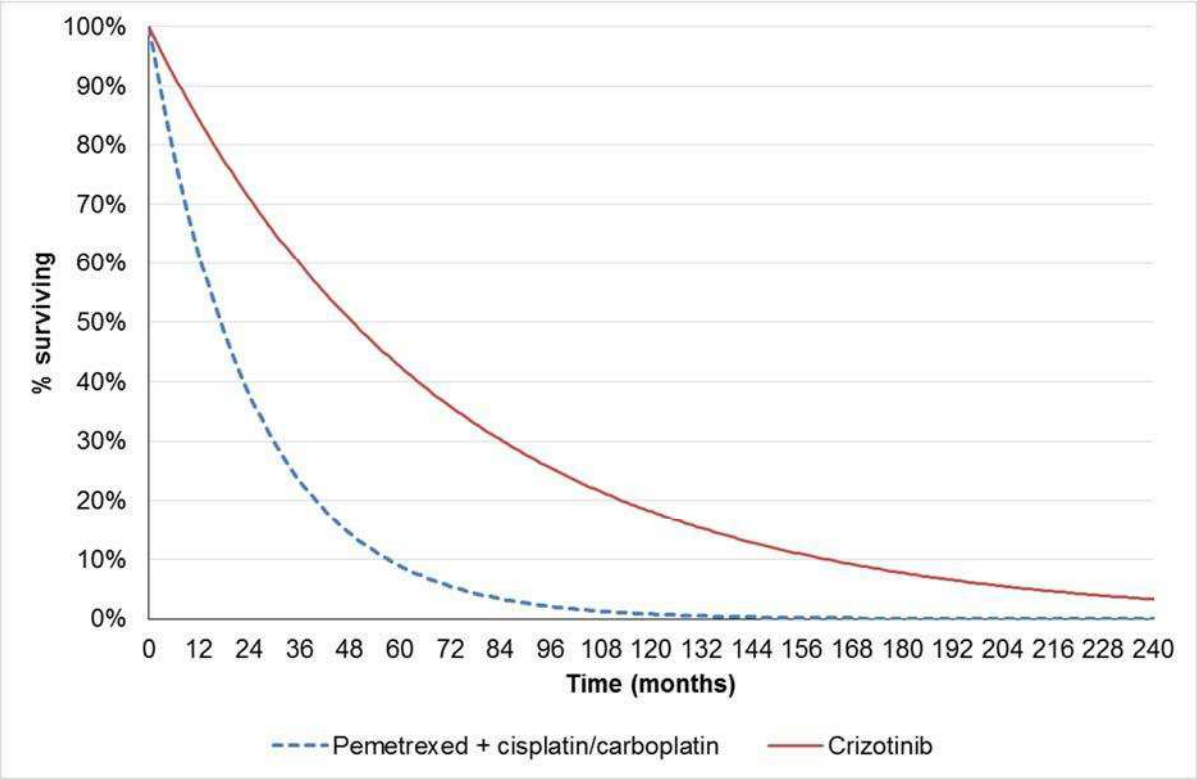


Figure 7 Company model first-line PROFILE 1001 scenario analysis OS

Source: company model

The final OS curves used in the company's subsequent-line PROFILE 1001 scenario analysis are shown in Figure 8. Mean OS in the company's subsequent-line PROFILE 1001 scenario analysis model is 69.0 months for treatment with crizotinib and 27.9 months for treatment with docetaxel, which yields an OS gain of 41.0 months.

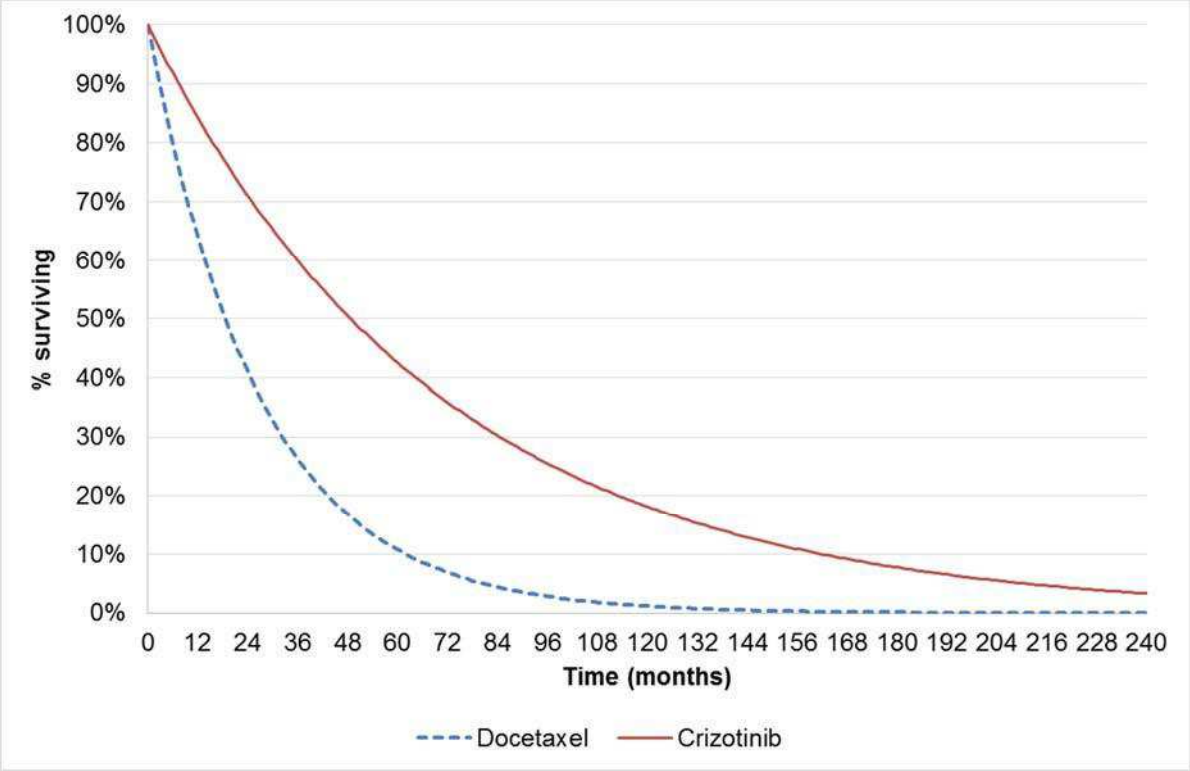


Figure 8 Company model subsequent-line PROFILE 1001 scenario analysis OS

Source: company model

Progression-free survival (comparators)

The company estimated PFS for treatment with pemetrexed+platinum therapy in the first-line setting using the inverse of the HR from the PROFILE 1014 PFS analysis (HR= [redacted] applied to the chosen exponential curve for treatment with crizotinib.

The company used the inverse of the crossover-adjusted HR from the pooled chemotherapy arm of the PROFILE 1007 trial (HR=2.05, CI: 1.57 to 2.70) to estimate PFS for treatment with docetaxel in the subsequent-line setting. Although the HR for the docetaxel subgroup was available from the PROFILE 1007 trial for PFS, the company used the HR from the pooled chemotherapy arm to maintain consistency with the modelling of OS. The company used the HR for the docetaxel subgroup in a scenario analysis (Table 23).

Table 23 PFS HRs from PROFILE 1007 used in the PROFILE 1001 scenario analysis (subsequent-line setting)

	PROFILE 1007 (chemotherapy)	PROFILE 1007 (docetaxel)
HR (95% CI)	0.49 (0.37 to 0.64)	0.30 (0.21 to 0.43)
Inverse HR applied to the crizotinib PFS curve (95% CI)	2.05 (1.57 to 2.70)	3.33 (2.33 to 4.76)

CI=confidence interval; HR=hazard ratio; PFS=progression-free survival
Source: CS, Table 37

The final PFS curves used in the company's first-line PROFILE 1001 scenario analysis are shown in Figure 9. Mean PFS in the company's first-line PROFILE 1001 scenario analysis model is 34.3 months for treatment with crizotinib and 16.1 months for treatment with pemetrexed+platinum, which yields a PFS gain of 18.2 months.

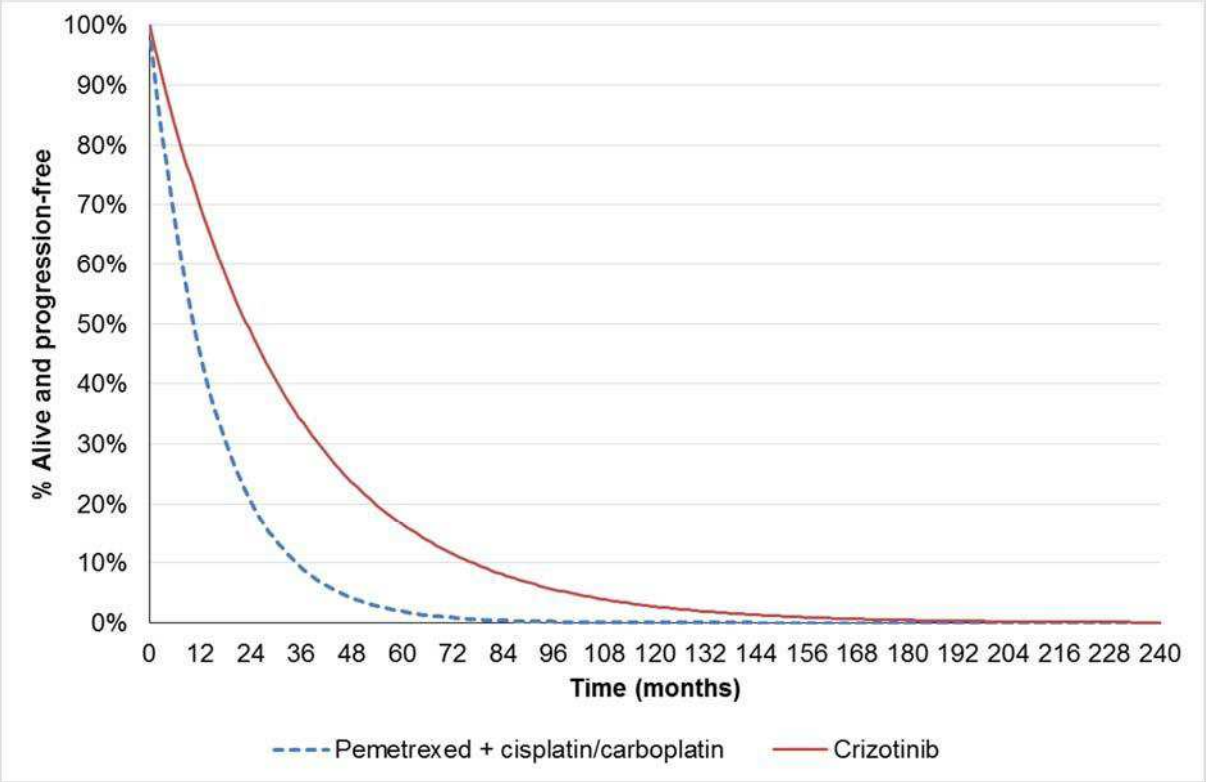


Figure 9 Company model first-line PROFILE 1001 scenario analysis PFS

Source: company model

The PFS curves used in the company's subsequent-line PROFILE 1001 study scenario analysis are shown in Figure 10. Mean PFS in the company's subsequent-line PROFILE 1001 study scenario analysis model is 34.3 months for treatment with crizotinib and 17.2 months for treatment with docetaxel, which yields a PFS gain of 17.1 months.

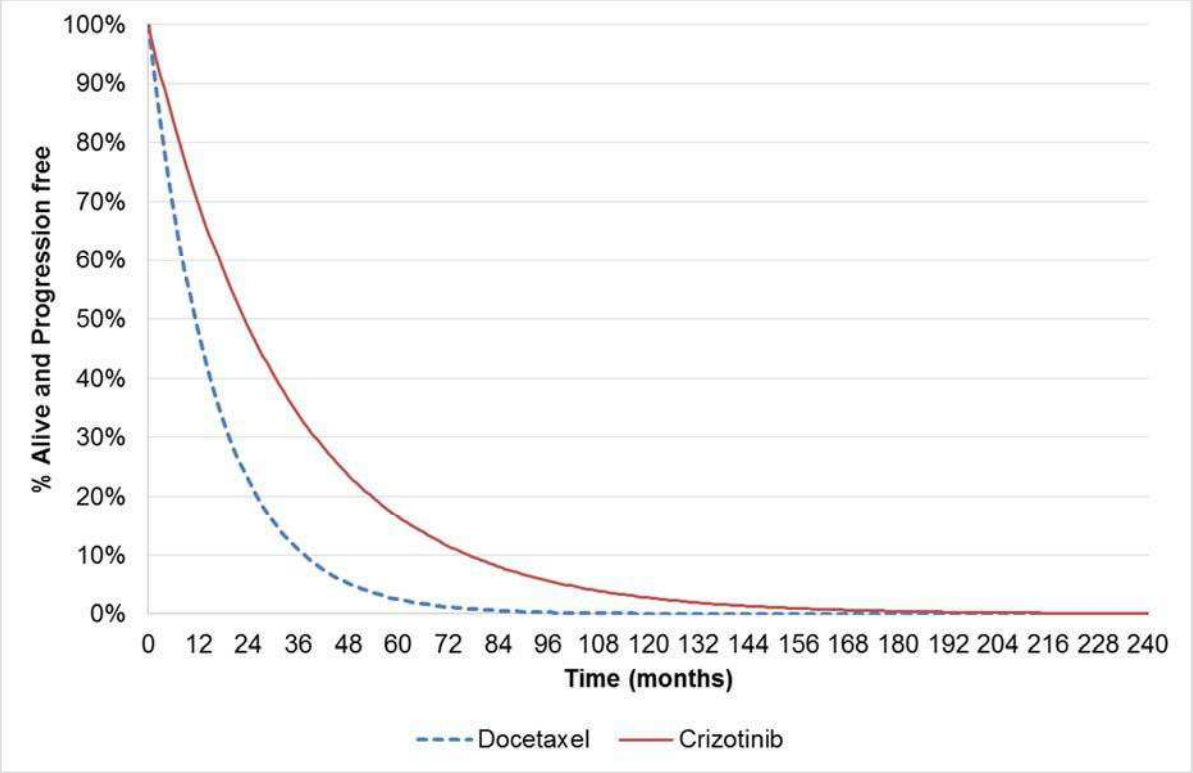


Figure 10 Company model subsequent-line PROFILE 1001 scenario analysis PFS

Source: company model

Time to treatment discontinuation (comparators)

A maximum of six cycles of treatment was assumed for treatment with pemetrexed+platinum therapy in the first-line setting. A maximum of three cycles of treatment was assumed for treatment with docetaxel in the subsequent-line setting.

Mean TTD in the company's first-line PROFILE 1001 scenario analysis model is 36.2 months for treatment with crizotinib and 3.8 months for treatment with pemetrexed+platinum.

Mean TTD in the company's subsequent-line PROFILE 1001 scenario analysis model is 36.2 months for treatment with crizotinib and 1.9 months for treatment with docetaxel.

5.4.6 Health-related quality of life

HRQoL data for treatment with crizotinib in patients with ROS1+ advanced NSCLC were not collected during the PROFILE 1001 study. Instead, the company used utility data collected from the PROFILE 1014 and PROFILE 1007 trials (these data were used in TA406 and TA422) on the assumption that HRQoL data from the ALK+ advanced NSCLC population would be an appropriate proxy for HRQoL for the ROS1+ advanced NSCLC population. Utility data were collected in the PROFILE 1014 and PROFILE 1007 trials using the EQ-5D questionnaire.

In the first-line model, PFS utility values were calculated using a mixed-effects analysis of the EQ-5D results from the PROFILE 1014 trial. The company calculated the mean first-line PFS utility value to be 0.81 for treatment with crizotinib and 0.72 for treatment with pemetrexed+platinum therapy. These PFS utility values are applied in the first-line model to all patients in the pre-progression state whilst receiving or following treatment, as well as to patients being treated with crizotinib beyond progression. The mean utility value used for the progressed state (treatment with docetaxel) in the first-line model is the same as the PFS utility value for treatment with docetaxel in the subsequent-line model. The utility value used in the model for patients who progress from docetaxel into third-line BSC is 0.473, which was taken from a paper by Nafees.[86]

Mean PFS utility values in the subsequent-line model were derived from a paper reporting patient-reported outcomes from the PROFILE 1007 trial.[87] The mean reported PFS utility value from the PROFILE 1007 trial was 0.82 for treatment with crizotinib and 0.66 for treatment with docetaxel. However, the company states that it is unlikely that HRQoL for PFS in subsequent-line treatment with crizotinib is higher than for first-line treatment with crizotinib, and as such has adjusted the utility value for PFS for crizotinib in the subsequent-line model to match the PFS utility in the first-line model (0.81). As in the first-line model, the subsequent-line PFS utility values are applied to all patients in the pre-progression state whilst receiving or following treatment, as well as to patients being treated with crizotinib beyond progression. Patients who progress (or discontinue treatment with crizotinib post-progression) are assumed to move into BSC with a utility value of 0.473.

The company notes that PFS utility values in both the first- and subsequent-line models for treatment with crizotinib are higher than those for the relevant comparators. The company justifies this by stating that treatment with crizotinib reduces symptoms of the disease more so than chemotherapy, and that it is associated with fewer and less severe side effects. A summary of all the utility values used in the first- and subsequent-line models is shown in Table 24

Utility values are taken directly from the PROFILE 1007 and PROFILE 1014 trials and have not been adjusted for AEs.

Table 24 Summary of utility values used for the cost effectiveness analysis in company model

State	Utility value: mean (SE)	95% CI
First-line model		
Treatment with crizotinib	0.81 (0.01)	(0.79 to 0.82)
Progression-free: pemetrexed+platinum therapy	0.72 (0.01)	(0.70 to 0.74)
Progressed (first time): docetaxel	0.66 (0.02)	(0.58 to 0.74)
Progressed (second time): BSC	0.47 (0.05)	(0.38 to 0.56)
Subsequent-line model:		
Treatment with crizotinib	0.81 (0.01)	(0.79 to 0.82)
Progression free: docetaxel	0.66 (0.02)	(0.58 to 0.74)
Progressed (first time): BSC	0.47 (0.05)	(0.38 to 0.56)

BSC=best supportive care; NSCLC=non-small cell lung cancer; SE=standard error
Source: adapted from CS, Table 40

5.4.7 Resources and costs

Drug acquisition costs

The company based resource use and unit costs for the economic models on several sources, including data from: PROFILE 1007 and PROFILE 1014 trials, national databases, previous technology appraisals of crizotinib in first- and subsequent-line ALK+ advanced NSCLC and clinical advice. Full details of the systematic review that was carried out to identify relevant cost and healthcare resource utilisation data are presented in Appendix I of the CS. The drug acquisition costs used in the company model are detailed in Table 25.

Table 25 Unit costs of interventions and comparators in the company models

Treatment	Unit	Unit cost	Source	Dose per cycle (treatment cycle length)	Cost per treatment cycle
Crizotinib	60 x 200 mg tablets	£4,689.00 [redacted])	MIMS[88]	2 x 250 mg per day (30 days)	£4,689.00 [redacted]
	60 x 250 mg tablets	£4,689.00 [redacted])			
Pemetrexed	100 mg vial	£160.00		500 mg/m^2 = 500*1.73 = 866 mg (21 days)	£1,465.40 with wastage £1,385.40 without wastage
	500 mg vial	£800.00			
Cisplatin	10 mg (10 ml vial)	£1.99	eMIt[89]	75 mg/m^2 = 75*1.73 =130 mg (21 days)	£14.64 with wastage £10.97 without wastage
	50 mg (50 ml vial)	£6.48			
	100 mg (100 ml vial)	£8.45			
Carboplatin	50 mg (5 ml vial)	£3.25		Target AUC = 5, dose = 500 mg (21 days)[45]	£23.64 with wastage £22.66 without wastage
	150 mg (15 ml vial)	£7.49			
	450 mg (45 ml vial)	£20.39			
	600 mg (60 ml vial)	£27.89			
Docetaxel	20 mg (1 ml vial)	£3.85		75mg/m^2 = 75*1.80 =135 mg (21 days)	£20.59 with wastage £17.25 without wastage
	80 mg (4 ml vial)	£12.39			
	140 mg (7 ml vial)	£20.62			
	160 mg (8 ml vial)	£20.44			

PAS=patient access scheme; *with PAS
Source: adapted from CS, Table 41

Crizotinib costs in the first- and subsequent-line models are applied according to the proportion of patients on treatment in each cycle according to TTD data from the relevant trials (as used in TA406 and TA422).

Pemetrexed+platinum therapy costs in the first-line model are applied according to the proportion of patients on treatment in each cycle according to TTD data from the PROFILE 1014 trial (as used in TA406). The company has modelled concomitant platinum therapy in the base case using on the proportions observed in the PROFILE 1014 trial: cisplatin (54%) or carboplatin (46%) as per the investigator's choice. Alternative proportions are investigated in a sensitivity analysis.

Docetaxel costs in the subsequent-line model are applied on the assumption that treatment is received for a maximum of three cycles, based on a median PFS of 2.6 months in the PROFILE 1007 trial.

Dosing

Standard treatment with crizotinib is 500 mg daily (250 mg tablets twice a day) for all patients.

Dosing for pemetrexed, cisplatin and docetaxel is based on body surface area (BSA). The company has used the BSA from TA406 (1.73m^2) in the base case first-line model for treatment with pemetrexed and with cisplatin. It has used the BSA from TA422 (1.80m^2) in the base case subsequent-line model. In the scenario analysis using time-to-event data from PROFILE 1001, the company has assumed a BSA of 1.80m^2 for comparator treatments for both lines of treatment.

Dosing for carboplatin is based on a target area under the concentration versus time curve (AUC in mg/mL/min). No information on the dose of carboplatin was reported for the PROFILE 1007 or 1014 trials, so the company reviewed other NICE STAs to reach AUC estimates of 5 mg/mL/min or 6 mg/mL/min, which translate to doses of 500 mg or 750 mg respectively. The company has assumed a target AUC for carboplatin of 5 mg/mL/min in the model, which translates to a dose of 500 mg.

Wastage

The company has assumed drug wastage in the base case analysis for all treatments except for crizotinib.

Drug administration costs

The company has assumed a dispensing cost associated with 12 minutes of pharmacist time for crizotinib (£14.59, uplifted from £14.40 in PSSRU 2015[90] to 2016 prices using the Hospital and Community Health Service index), since it is an oral therapy that does not require hospital administration.

Cisplatin-containing regimens were assumed to incur a day-case administration appointment, whereas carboplatin-containing regimens and docetaxel monotherapy were assumed to incur an outpatient administration appointment. Drug administration costs for all treatments used in the company model are shown in Table 26.

Table 26 Drug administration costs in the company model for crizotinib and comparators

Treatment	Setting	Cost code	Description	Unit cost
Crizotinib	N/A	N/A	Dispensing cost (12 minutes pharmacist time)	£14.59
Pemetrexed plus cisplatin	Day case and regular day/night	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£406.63
Pemetrexed plus carboplatin	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30
Docetaxel	Outpatient	SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£304.30

Source: CS, Table 42

Health state resource use and costs

The company has assumed that the health state and monitoring costs associated with progression-free (first- and subsequent-line models) and progressed disease (receiving therapy) states are the same. It has assumed that patients receiving BSC in the first- and second-line models use the same health state and monitoring resources, which are different from those in the progression-free and progressed (receiving therapy) states. Resource use assumptions were sourced from TA406 and TA296 (superseded by TA422). The costs associated with these health states are shown in Table 27.

Table 27 Health states and associated costs in the company model

Health state	Resources Required	Frequency per month (from TA406)	Unit cost	Reference
Patients in progression-free health state and patients in progressed disease health state receiving second-line treatment	Outpatient Visit	0.75	£151.12	NHS reference costs 2015-16 Outpatient Attendances Data - medical oncology (370) [91 91 91 91 89 89 93 92 90 90 78 78]
	GP visit	10% patients (1 visit)	£27.00	PSSRU 2016 - Clinic consultation lasting 9.22 minutes without qualification costs
	Cancer nurse	20% patients (1 visit)	£69.20	NHS reference costs 2015-16 Nurse cancer relate adult face-to-face (N10AF)
	Complete Blood Count	0.75	£3.10	NHS reference costs 2015-16 Direct Access: Pathology Services (DAPS05)
	Biochemistry	0.75	£1.18	NHS reference costs 2015-16 Direct Access: Pathology Services (DAPS04)
	CT scan	30% patients (0.75 scans)	£132.19	NHS reference costs 2015-16 Direct Access: Pathology Services (RD26Z) [91 91 91 91 89 89 93 92 90 90 78 78]
	Chest X-ray	0.75	£30.26	NHS reference costs 2015-16 Direct Access Plain Film (DAPF)
Total cost per month (first- and subsequent-line treatment)			£185.53	
Patients in progressed disease health state receiving third-line treatment	Oncologist Visit	1 visit	£151.12	NHS reference costs 2015-16 Outpatient Attendances Data - medical oncology (370) [91 91 91 91 89 89 93 92 90 90 78 78]
	GP visits	28% patients	£27.00	PSSRU 2016 - Clinic consultation lasting 9.22 minutes without qualification costs
	Cancer nurse	10% patients (1 visit)	£69.20	NHS reference costs 2015-16 Nurse cancer relate adult face-to-face (N10AF)
	Complete Blood Count	100% patients	£3.10	NHS reference costs 2015 -16 Direct Access: Pathology Services (DAPS05)
	Biochemistry	100% patients	£1.18	NHS reference costs 2015-16 Direct Access: Pathology Services (DAPS04)
	CT scan	5% patients (0.75 scans)	£132.19	NHS reference costs 2015-16 Direct Access: Pathology Services (RD26Z) [91 91 91 91 89 89 93 92 90 90 78 78]
	X-ray	30% patients (0.75 scans)	£30.26	NHS reference costs 2015-16 Direct Access Plain Film (DAPF)
Total cost per month, progressed disease			£181.65	

BSC=best supportive care; CT=computed tomography
Source: adapted from CS, Table 47

The model includes a one-off cost for palliative care in the 90 days before death. This cost of terminal care includes district nurse, nursing, residential and hospice care, and Marie Curie nursing (Table 28). The cost of terminal care is estimated to be £7,415 and is applied as a one-off cost at the point of death.

Table 28 Cost of palliative care in the company model

Cost	Unit cost	Reference	2015/16 Uplifted cost (PSSRU 2016)[92]
District nurse	£278	Georghiou and Bardsley[93]	£298
Nursing and residential care	£1,000		£1,106
Hospice care – inpatient	£550		£590
Hospice care – final 3 months of life	£4,500		£4,830
Marie Curie nursing service	£550		£590
Total cost			£7,415

Source: CS, Table 48

ROS1 testing

The company notes that the introduction of crizotinib to treat ROS1+ advanced NSCLC would require additional resource for ROS1 testing. The company has considered upfront testing (alongside ALK and EGFR testing) in the base case analysis and sequential testing (after patients have been found to be negative for ALK and EGFR rearrangements) in a scenario analysis. The company has assumed that there will be no impact of ROS1 testing on resource costs other than the purchase of the tests as the NHS already has the infrastructure in place to carry out the testing. It has also assumed that all patients who will be tested for ROS1 rearrangements have non-squamous NSCLC.

The company has used a reported prevalence of 1.8% for ROS1 rearrangements amongst patients with adenocarcinoma[9] and a prevalence of 93.9% for adenocarcinoma amongst patients with non-squamous NSCLC. This results in a calculated prevalence of 1.69% for ROS1 rearrangements amongst patients with non-squamous NSCLC.

Testing for ROS1 is modelled as IHC followed by confirmatory FISH. The company has used the reported specificity (83%) and sensitivity (100%) of the IHC test[94] to estimate the proportion of patients who would go on to receive the FISH test after the IHC test. It has assumed that 100% of patients receiving the FISH test would be diagnosed accurately.

The company base case analysis includes testing for ROS1 rearrangements upfront, meaning that all patients with non-squamous NSCLC would be tested using IHC. All patients with non-squamous NSCLC who test positive with IHC will then be tested with FISH. The company estimates that 18.69% of patients tested with IHC will test positive for ROS1 (1.69% who have ROS1 and 17% [100-83%] who test false positive). Patients who test positive using IHC will

then be tested with FISH, which then will result in 1.69% of patients originally tested testing positive for ROS1. The total estimated costs of up front testing for ROS1 rearrangements in the non-squamous NSCLC population is £4,288 per patient correctly diagnosed (Table 29).

Table 29 Company estimate of upfront ROS1 testing cost (base case)

Item	Cost per test	% of non-squamous patients receiving test	Total cost
IHC test	£50[95]	100%	£50
FISH test	£120[96]	1.69% (% ROS1) + 17% (% false positive IHC) = 18.7%	£120 * 18.7% = £22.44
		Total cost per testing	£50 + £22.44 = £72.44
		Total cost per ROS1+ patient diagnosed	£72.44 / 1.69% = £4,287.92

IHC= ImmunoHistoChemistry; FISH=fluorescence in situ hybridization
Source: adapted from CS, Table 53

Adverse events

In the base case analysis, the company has included resource use and costs in the model due to Grade 3 and Grade 4 AEs occurring in ≥5% of patients in the PROFILE 1007 and PROFILE 1014 trials. These AEs were elevated transaminases, neutropenia, anaemia, leukopenia, thrombocytopenia, and pulmonary embolism. In the scenario analysis using the results of the PROFILE 1001 study, hypophosphatemia was also included. Costs related to AEs are applied as a one-off cost in the first cycle of the model.

The resource use and costs associated with managing each AE used in the company model are given in Table 30.

Table 30 Cost of treating adverse events in company model

Adverse event	Resource required	Source	Unit cost	Total cost	Reference for unit cost
Anaemia	1.7 hospitalisation days	Consistent with TA296 (replaced by TA422) and TA406	£335.57 per day	£570.47	NHS reference costs 2015/16; Iron Deficiency Anaemia with CC Score 0-1 SA04L
Thrombocytopenia	2.0 hospitalisation days		£303.52 per day	£607.04	NHS reference costs 2015/16; Thrombocytopenia with CC Score 0-1 SA12K
Neutropenia	Managed by dose reduction		-	-	-
Leukopenia	Managed by dose reduction (assumption)		-	-	-
Elevated transaminases	Managed by dose reduction		-	-	-
Hypophosphatemia	1 hospitalisation day	Assumption	£287.19 per day	£287.19	NHS reference costs 2015/16; Fluid or Electrolyte disorders, without interventions CC Score 0-1 KC05N
Pulmonary embolism	1 hospitalisation day	Assumption	£26.34 per day	£26.34	NHS reference costs 2015/16; Weighted average of Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4 (YR23B) and Anticoagulant Services (Total Outpatient Attendances)

CC=complication and comorbidity
Source: adapted from CS, Table 50

5.4.8 Cost effectiveness results

The company's base case estimates of total costs, life years gained (LYG), QALYs and ICERs per QALY gained for the comparison of the cost effectiveness of first-line treatment with crizotinib versus pemetrexed+platinum and subsequent-line treatment with crizotinib versus docetaxel monotherapy are shown in Table 31. The ERG reiterates that the company's base case estimates for first- and subsequent-line treatment with crizotinib use data from patients with ALK+ advanced NSCLC population as a proxy for data from patients with ROS1+ advanced NSCLC patients.

Base case analysis

In the first-line base case analysis, treatment with crizotinib generates incremental LYG (+2.39 years) and more benefits (+1.28 QALYs) than treatment with pemetrexed+platinum at an increased cost of [redacted]. The company base case ICER for the comparison of first-line treatment with crizotinib versus pemetrexed+platinum is [redacted] per QALY gained.

In the subsequent-line base case analysis, treatment with crizotinib generates incremental LYG (+1.36 years) and more benefits (+0.93 QALYs) than treatment with docetaxel at an increased cost of [redacted]. The company base case ICER for the comparison of subsequent-line treatment with crizotinib versus docetaxel is [redacted] per QALY gained.

PROFILE 1001 scenario analysis

In the first-line scenario analysis, treatment with crizotinib generates incremental LYG (+3.60 years) and more benefits (+1.95 QALYs) than treatment with pemetrexed+platinum at an increased cost of [redacted]. The company base case ICER for the comparison of first-line treatment with crizotinib versus pemetrexed+platinum is [redacted] per QALY gained.

In the subsequent-line scenario analysis, treatment with crizotinib generates incremental LYG (+3.43 years) and more benefits (+1.95 QALYs) than treatment with docetaxel at an increased cost of [redacted]. The company base case ICER for the comparison of subsequent-line treatment with crizotinib versus docetaxel is [redacted] per QALY gained.

Table 31 Company deterministic cost effectiveness results: base case and PROFILE 1001 study scenario analysis (with crizotinib PAS)

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY gained)
Base case: first-line							
Pemetrexed+platinum	£23,267	1.47	0.84				
Crizotinib	[redacted]	3.86	2.13	[redacted]	2.39	1.28	[redacted]
Base case: subsequent-line							
Docetaxel	£11,076	1.39	0.71				
Crizotinib	[redacted]	2.75	1.63	[redacted]	1.36	0.93	[redacted]
Scenario analysis (PROFILE 1001): first-line							
Pemetrexed+platinum	£22,570	2.15	1.29				
Crizotinib	[redacted]	5.75	3.25	[redacted]	3.60	1.95	[redacted]
Scenario analysis (PROFILE 1001): subsequent-line							
Docetaxel	£12,706	2.32	1.29				
Crizotinib	[redacted]	5.75	3.24	[redacted]	3.43	1.95	[redacted]

ICER=incremental cost effectiveness ratio; LYG=life years gained; PAS=patient access scheme; Inc=incremental; QALY=quality adjusted life year
Source: CS, Table 62-65

5.4.9 Sensitivity analyses

Deterministic sensitivity analysis

The company carried out one-way sensitivity analyses to explore the sensitivity of model results to variations in the magnitude of various model inputs. The results from the first- and subsequent-line models in the base case and PROFILE 1001 scenario analysis are presented in Figures 40 to 43 of the CS.

Results from the company first-line base case model show that varying the TTD and OS parametric model coefficients for crizotinib has the biggest effect on the company's cost effectiveness results. Results from the subsequent-line base case model show that varying the HR for OS has the biggest effect on the company's cost effectiveness results, followed by varying the covariates for OS and PFS, and utility values for treatment with docetaxel and BSC.

Results from the company's first-line PROFILE 1001 study scenario analysis show that varying the HR for OS has the biggest effect on the company's cost effectiveness results, followed by varying the covariates for OS, PFS and TTD, and the utility value for BSC. Results from the subsequent-line PROFILE 1001 study scenario analysis model show that, as in the first-line scenario analysis, varying the HR for OS has the biggest effect on the company's cost effectiveness results, followed by varying the covariates for OS, PFS and TTD, and the utility value for BSC.

Probability sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to derive the mean ICER per QALY gained in the first- and subsequent-line base case and scenario analysis. The PSA was run for 10,000 iterations. Results from the PSA are shown in Table 32.

The probabilistic ICER per QALY gained in the company first-line base case for crizotinib versus pemetrexed+platinum is [redacted] (deterministic ICER = [redacted]. The probabilistic ICER per QALY gained in the company subsequent-line base case for crizotinib versus docetaxel is [redacted] (deterministic ICER = [redacted].

The probabilistic ICER per QALY gained in the company first-line PROFILE 1001 scenario analysis for crizotinib versus pemetrexed+platinum is [redacted] (deterministic ICER = [redacted]. The probabilistic ICER per QALY gained in the company subsequent-line PROFILE 1001 scenario analysis for crizotinib versus docetaxel is [redacted] (deterministic ICER = [redacted].

Table 32 Company probabilistic cost effectiveness results: base case and PROFILE 1001 study scenario analysis (with crizotinib PAS)

Technologies	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY gained)
Base case: first-line (deterministic ICER = [redacted])							
Pemetrexed+platinum	£22,529	1.50	0.86				
Crizotinib	[redacted]	3.93	2.17	[redacted]	2.43	1.31	[redacted]
Base case: subsequent-line (deterministic ICER = [redacted])							
Docetaxel	£11,092	1.40	0.71				
Crizotinib	[redacted]	2.76	1.63	[redacted]	1.37	0.92	[redacted]
Scenario analysis (PROFILE 1001): first-line (deterministic ICER = [redacted])							
Pemetrexed+platinum	£22,913	2.41	1.39				
Crizotinib	[redacted]	5.82	3.34	[redacted]	3.42	1.95	[redacted]
Scenario analysis (PROFILE 1001): subsequent-line (deterministic ICER = [redacted])							
Docetaxel	£13,378	2.83	1.47				
Crizotinib	[redacted]	5.82	3.33	[redacted]	2.99	1.86	[redacted]

ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life year
Source: CS, Table 66, Table 67, Table 68, Table 69

5.4.10 Model validation and face validity check

The company undertook a number of steps to try to ensure the validity of its models:

- Comparison of outcomes with previous appraisals, and outcomes from trials and published literature
- Clinical expert validation of the results of survival modelling
- Quality control of the economic model by model developers on behalf of the company.

5.5 Detailed critique of the company's economic model

5.5.1 NICE Reference Case checklist

Table 33 NICE Reference Case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partial. Data from the ALK+ advanced NSCLC population was used as proxy data for ROS1+ advanced NSCLC patients in the base case analyses
Comparator(s)	Alternative therapies routinely used in the NHS	Partial. Pemetrexed+platinum therapy is the only comparator included in the cost effectiveness analysis for first-line treatment. Docetaxel monotherapy (based on a mix of pemetrexed or docetaxel monotherapy) is the only comparator included in the cost effectiveness analysis for subsequent-line treatment
Perspective costs	NHS and PSS	Partial. PSS costs were not fully considered in the CS
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes. Time horizon of 20 years
Synthesis of evidence on outcomes	Systematic review	Yes. The company uses data from the PROFILE 1001 study and PROFILE 1007 and 1014 trials
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standard and validated instrument	Yes
Benefit valuation	Time-trade off or standard gamble	Yes. Time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes. The company undertook a probabilistic sensitivity analysis

HRQoL=health-related quality of life; NSCLC=non-small cell lung cancer; PSS=Personal Social Services; QALY=quality adjusted life year

5.5.2 Drummond checklist

Table 34 Drummond critical appraisal checklist completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	Evidence of effectiveness based on data from the ALK+ advanced NSCLC population as a proxy for data for ROS1+ advanced NSCLC patients
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partial	Cost of treating some AEs may have been underestimated
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Partial	The company undertook a probabilistic sensitivity analysis in the first- and subsequent-line base case analysis and scenario analysis. The model lacked the facility to change assumptions previously accepted by an Appraisal Committee
Did the presentation and discussion of study results include all issues of concern to users?	Partial	The company did not provide adequate rationale for some of the assumptions made

AEs=adverse events; ERG=Evidence Review Group; NSCLC=non-small cell lung cancer

5.6 ERG critique of the company's economic model

5.6.1 Fundamental issues in the economic analysis

There are several fundamental issues that prevent the ERG from providing a detailed critique of the submitted cost effectiveness models in this ERG report. The ERG's principal concern is that it has been unable to check and verify many of the inputs into the economic models submitted by the company. The ERG has been unable to verify whether the models appropriately address the decision problem set by NICE for two key reasons:

1. The CS relies heavily on the assumptions and modelling approaches used in three previous STAs (TA406, TA422 and TA296). The company has not provided sufficient justification in the CS for the application of these assumptions and approaches in the current appraisal, beyond the fact that they were previously accepted. The ERG considers that assumptions accepted in a previous STA should not be reused unquestioningly as the context in which those assumptions were preferred may have changed. In addition,

the ERG views this appraisal as being independent from previous appraisals of crizotinib in advanced NSCLC – it is neither an update nor a review – and therefore the ERG considers that the CS should be written as a stand-alone document.

For example, the Appraisal Committee in TA422 preferred one of the ERG's scenarios for modelling OS over the company's base case modelling. This scenario has been presented as the base case model for subsequent-line OS in this STA without any justification, other than that it was the preferred approach in TA422. In TA422 the ERG had to explore alternative scenarios for modelling OS because the company did not provide sufficient information about the crossover adjustment that was performed and, without the additional information, the ERG could not fully critique the method. The ERG does not consider it appropriate to simply assume that the method preferred in TA422 is the best possible method for estimating OS for subsequent-line treatment in an ALK+ NSCLC population especially when the Appraisal Committee preferred the previous ERG's method due to the lack of information provided by the company. The company could have provided the missing information in the current CS to allow the ERG to properly review the crossover-adjustment method, but they did not.

2. Even if the ERG were able to verify the assumptions made by the company, lack of model functionality would impede the ERG's ability to investigate the effects of specific key assumptions in the model.

   For example, in the base case analysis, the time-to-event estimates from the PROFILE 1014 trial that were used to model outcomes for first-line treatment were adjusted for baseline characteristics, as the baseline characteristics in the PROFILE 1014 trial were not considered to be representative of patients with ALK+ advanced NSCLC seen in NHS clinical practice. This approach was considered appropriate by the Appraisal Committee in TA406. However, the company has not built into the first-line model the same function for the associated PFS and TTD estimates, which means that the overall effect on the first-line base case ICER per QALY gained of removing the baseline-characteristics adjustment cannot be easily investigated.

The issues the ERG has had with verifying the model have been compounded by the company's submission of updated models during the appraisal process. This update was submitted as a result of a mistake identified by the company which it says has no impact on the ICER per QALY gained. However, the ERG is not able to say whether the company's

changes would impact the ICERs per QALY gained yielded as a result of the ERG's amendments to the model.

The ERG understands that NICE is currently undertaking a consultation process to develop a quality assurance checklist that will be used by ERGs to validate company models. The ERG agrees that quality assurance is an important aspect of the STA process and is necessary to allow Appraisal Committees to make informed decisions. The appraisal of crizotinib for ROS1+ advanced NSCLC includes two company models that cannot be fully quality assured for the reasons outlined above. This also means that the ERG cannot be confident that the results of any additional exploratory analyses are reliable. As a result, the critique and information provided in this ERG report is limited and the ERG is unable to provide ERG preferred base case ICERs per QALY gained.

5.6.2 Key company modelling assumptions

The company base case analysis is founded on the assumption that the outcomes of treatment with crizotinib in an ALK+ advanced NSCLC population are an appropriate proxy for the outcomes of treatment with crizotinib in a ROS1+ advanced NSCLC population. This assumption is discussed in Section 2.1. The company has included a scenario analysis that uses data from a ROS1+ advanced NSCLC population in the single-arm PROFILE 1001 study. The company claims that the results of this scenario analysis help to reduce uncertainty in decision making by demonstrating that crizotinib is also cost effective when the limited data available are used directly to model treatment for the ROS1+ advanced NSCLC population. The ERG has therefore examined the company's PROFILE 1001 study scenario analysis as well as the base case model in order to test the robustness of the company's cost effectiveness results.

The company has also assumed that 'pooled chemotherapy' is a suitable proxy for treatment with docetaxel in the subsequent-line model. This assumption has not been investigated in the cost effectiveness analysis by the ERG.

5.6.3 Major modelling issues

First- and subsequent-line treatments with crizotinib in an ALK+ advanced NSCLC population have been previously appraised by NICE (TA406, TA422 and TA296); therefore, much of the data and modelling included in the company base case analysis has been discussed in previous STAs (Table 35). The ERG has prioritised the critique of newly available data in this appraisal (updated OS from the PROFILE 1014 trial and data from the PROFILE 1001 study). However, this does not imply that the ERG is satisfied that inputs and approaches not covered in this critique are appropriate and properly implemented in the model.

Table 35 Previous appraisals featuring selected model inputs used in this STA

Model	Outcome	Previous appraisal
First-line base case	OS	Updated from TA406
	PFS	TA406
	TTD	TA406
	Utility	TA406
Subsequent-line base case	OS	TA422
	PFS	TA296 and TA422
	TTD	TA422
	Utility	TA406 and TA422
PROFILE 1001 scenario analysis	OS	New
	PFS	New
	TTD	New
	Utility	TA406 and TA422

PFS=progression-free survival; OS=overall survival; TTD=time-to-treatment discontinuation

Post-progression survival – first-line base case

The company's first-line base case model yields a substantial PPS benefit for treatment with crizotinib versus pemetrexed+platinum. Comparing PPS for treatment with crizotinib (29.6 months) and pemetrexed+platinum (10.4 months) results in a 19.2 month PPS gain for patients treated with crizotinib. This PPS gain is compared to a PFS gain of 9.5 months for treatment with crizotinib (16.8 months) versus pemetrexed+platinum (7.3 months). This means that the extra survival gained beyond progression constitutes 67% of total OS gain for treatment with crizotinib (Table 36). This suggests that the treatment effect is better after progression (and after patients have stopped treatment) than before progression and therefore that OS treatment effect is better than PFS treatment effect. The ERG does not consider this modelled outcome to be supported by the evidence from the trial nor by the literature.

Table 36 First-line base case: overall survival breakdown by health state

Health state	Crizotinib (months)	Pemetrexed+platinum (months)	Increment (months)	Increment
Pre-progression	16.8	7.3	9.5	33.3%
Post-progression	29.6	10.4	19.2	66.7%
Total	**46.4**	**17.7**	**28.7**	**100%**

Source: company model

There is evidence to suggest that it is plausible to assume (in the absence of robust evidence to the contrary) that the OS treatment effect might be expected to be similar to the PFS treatment effect in advanced NSCLC trials. As noted in section 4.3.2, the ERG in TA422 referred to an analysis by the FDA[78] which explored trial-level and patient-level associations between PFS and OS in advanced NSCLC trials (including crizotinib). The results of this analysis suggest that it is not unreasonable to assume similarity between PFS and OS treatment effects in the absence of other evidence.

The ERG acknowledges that there may be some PPS benefit attributable to treatment with crizotinib, not least because a substantial proportion of patients in the PROFILE 1014 trial continued to receive crizotinib after progression due to 'symptomatic benefit' (mean length of post-progression treatment in the model is 1.4 months). However, given that the magnitude of OS gain is unknown in the PROFILE 1014 trial due to trial immaturity and patient crossover, the ERG considers it questionable to model a PPS gain that is substantially larger than PFS gain (which translates into a greater OS treatment effect than PFS treatment effect).

Post-progression survival – subsequent-line base case

The company's subsequent-line base case model also yields a substantial PPS benefit for patients treated with crizotinib, although the proportion of OS gain attributable to PPS gain is smaller in the subsequent-line base case model than in the first-line model. Post-progression survival in the subsequent-line model is 22.5 months for treatment with crizotinib versus 11.8 months for docetaxel. This means that patients in the subsequent-line setting who are treated with crizotinib are expected to survive twice as long after progression when compared to patients treated with docetaxel. Post-progression survival gain is estimated in the company model to be twice as long as PFS gain, meaning that 65% of OS gain is attributable in the model to survival gained after progression (

Table 37). Again, this implies that the treatment effect is better after progression than before progression (and that OS treatment effect is greater than PFS treatment effect).

Table 37 Subsequent-line base case: overall survival breakdown by health state

Health state	Crizotinib (months)	Docetaxel (months)	Increment (months)	Increment
Pre-progression	10.6	4.9	5.7	34.8%
Post-progression	22.5	11.8	10.6	65.2%
Total	**33.0**	**16.7**	**16.3**	**100.0%**

Source: company model

The ERG again acknowledges that some patients are treated with crizotinib beyond progression in the subsequent-line setting and that this may indicate some prolonged benefit beyond progression. The company models treatment beyond progression in the subsequent-line base case to be 5.4 months. Clinical advice to the ERG is that it is plausible that patients at this stage in their treatment might receive 2 to 3 months of treatment with crizotinib beyond progression because there are few other treatment options available; however, an average of 5.4 months of treatment beyond progression is unlikely.

PROFILE 1001 study scenario analysis

In the CS, the company has mainly used data from a different population (ALK+ advanced NSCLC) to the population of interest because the data available for treatment with crizotinib in a ROS1+ advanced NSCLC population are limited. The company concluded that it was preferable to use data from larger RCT trials, albeit with immature OS, in an ALK+ advanced NSCLC population (PROFILE 1014 and PROFILE 1007 trials) than to use data from a small, immature, single-arm study in a ROS1+ advanced NSCLC population (PROFILE 1001 study). The ERG acknowledges that, for modelling purposes, more data are better than less. However, it also notes that the uncertainty inherent in the model as a result of the use of a proxy population (the extent to which the populations are similar is unknown) cannot be quantified or otherwise described, whereas uncertainty originating from poor quality data is more straightforward to articulate.

Since there were very few patients treated in the first-line setting in the PROFILE 1001 study, the company decided it was appropriate to pool first- and subsequent-line results and use the same 'all-lines' data to model first-and subsequent-line treatment in its PROFILE 1001 scenario analysis. The ERG agrees that the pooling of data seems appropriate given there were only seven patients in the first-line setting; however, the ERG notes that this approach adds to the uncertainty of any results based on data from the PROFILE 1001 study.

The company has attempted to fit parametric models to the 'all-lines' time-to-event data to estimate OS, PFS and TTD in the ROS1+ advanced NSCLC population, but concedes that

none of the fitted models have good face validity as is shown by the OS data depicted in Figure 11. One reason for the lack of visual fit of the parametric models is the immaturity of the trial data. Almost 70% of OS data from the PROFILE 1001 study is censored; thus the censored information has a much greater influence on the calculation of curve parameters than does the information about events that have been observed.

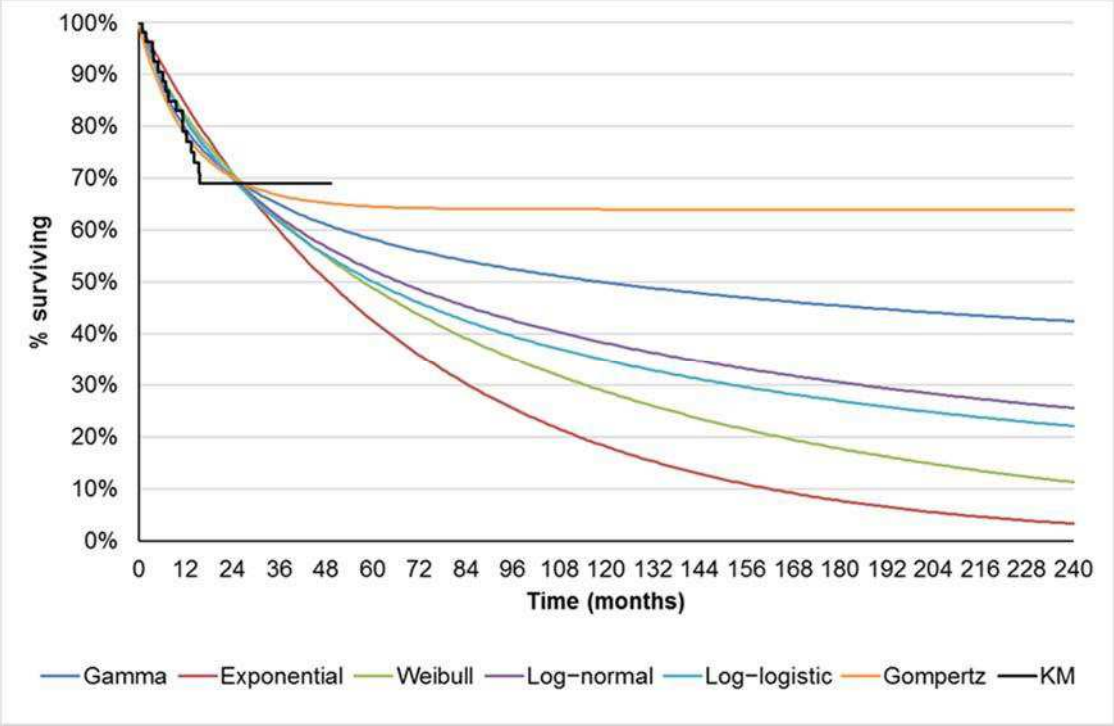


Figure 11 Company parametric curve fits to OS data from PROFILE 1001

Source: CS, Figure 24

As well as lacking face validity, the company's modelling of treatment with crizotinib from the PROFILE 1001 study results in very long survival projections in comparison to the base case analysis. Mean OS is 5.8 years in the company's PROFILE 1001 study scenario for treatment with crizotinib versus 3.9 years in the base case analysis. Mean PFS is estimated to be 2.9 years in the company's scenario versus 1.2 years in the base case analysis.

The company has created comparator time-to-event estimates by using HRs from the PROFILE 1014 and PROFILE 1007 trials. The OS HRs are based on RPSFTM crossover adjustments carried out by the company, which are critiqued in Section 4 of this report. The ERG does not consider these HRs to be appropriate, given that the modelling of crossover adjusted OS in the base case analysis results in implausible PPS estimates.

Progression-free utility values: first-line treatment

Although the EQ-5D scores from the PROFILE 1014 trial appear to show greater HRQoL benefit for treatment with crizotinib than for treatment with pemetrexed+platinum, the ERG is

concerned that the magnitude of that benefit is uncertain. This is due to the lack of long-term EQ-5D data for treatment with pemetrexed+platinum, the lack of a statistically significant difference between mean EQ-5D estimates for those cycles where data have been recorded and the potential influence of the open-label nature of the trial on patients' responses to the EQ-5D. The ERG has explored a range of cost effectiveness estimates bounded by the assumption of no HRQoL benefit for treatment with crizotinib. The ERG has also explored the impact of using a PFS utility value of 0.75 for treatment with pemetrexed+platinum. These analyses do not resolve the company's inconsistent use of data i.e., use of adjusted baseline characteristics for the time-to-event estimates and use of unadjusted utility values.

The ERG also notes that, although baseline EQ-5D values are similar in the two arms of the PROFILE 1014 trial, there is a substantial increase in the mean utility value (from 0.72 to 0.81) reported between baseline and cycle 2 in the crizotinib arm. This increase does not occur in the pemetrexed+platinum arm. The ERG is concerned that this sudden increase in utility in one arm and not the other may be explained to some extent by the open-label nature of the trial; that is, patients who know they are receiving the intervention may report feeling better than those receiving the comparator treatment. This concern is supported by the observation that cycle 2 is the only cycle in which there is a statistically significant difference ($p<0.05$) between mean EQ-5D values recorded in each arm of the PROFILE 1014 trial.

It is noted in the FAD for TA406 that the Appraisal Committee preferred the company's revised PFS utility estimate (0.75) for treatment with pemetrexed+platinum in the first-line setting, as it considered the 0.72 value used in the company's base case to be too low. The company in this STA has not explored the impact of using a PFS utility of 0.75 for treatment with pemetrexed+platinum in the first-line setting.

The ERG is also concerned that these utility values pertain to the unadjusted PROFILE 1014 trial population, whereas, in the first-line base case model, the time-to-event estimates have been adjusted to reflect the population observed in NHS clinical practice.

5.6.4 Minor modelling issues

Cost of pulmonary embolism

The company has estimated the cost of treating pulmonary embolism to be £26.34; this cost has likely been underestimated, as Hospital Episode Statistics[97] report mean time in hospital for pulmonary embolism to be 6 days. Also, no treatment costs are included in this estimate. NICE guidance on treating thromboembolism[98] indicates that patients should be initially treated for at least 5 days with a low molecular weight heparin (LMWH) and that a LMWH should be given for 6 months if a patient with active cancer develops a pulmonary embolism.

The impact of this underestimated cost on the size of the ICER per QALY gained is small, so the ERG has not amended the cost in the model.

Testing for ROS1 rearrangements

The company has assumed upfront testing in the base case analysis for both the first- and subsequent-line models. Clinical advice to the ERG is that only a small percentage of patients who are eligible to receive crizotinib as a subsequent-line treatment would not have already been tested for ALK and EGFR mutations earlier in their treatment pathway. The ERG therefore considers that it would be more appropriate to use the cost of sequential testing (ROS1 testing in EGFR- and ALK-negative population) in the subsequent-line setting. This has a small effect on the ICER per QALY gained.

The ERG notes that NHS laboratory services may offer a discount when testing for more than one mutation at the same time. The All Wales Genetic Laboratory list price to carry out FISH analysis (ALK) for lung cancer is £120 and the price for EGFR testing is £175 when undertaken in isolation; however, the cost to carry out ALK and EGFR tests at the same time is £250, which represents a 15% discount on the price of carrying out each of these tests individually. Therefore, it is plausible to assume that the upfront cost of carrying out FISH testing for ROS1 alongside other tests would be approximately £102 (£120 * 85%). This has a small effect on the ICER per QALY gained.

The final scope issued by NICE required that the company conduct a sensitivity analysis without the cost of the ROS1 diagnostic test. This sensitivity analysis has not been provided in the CS. However, the functionality exists in the company model to remove the cost of ROS1 testing. The ERG has also investigated the impact of removing the cost of ROS1 testing, which reduces the ICER per QALY gained in the first–line setting by [redacted] to [redacted] and reduces the ICER per QALY gained in the subsequent–line setting by [redacted] to [redacted].

5.6.5 ERG exploratory analyses

Overall survival: first-line treatment

As previously discussed, PPS gain in the company first-line base case model is implausibly large. This can be attributed to inappropriate estimates of either PFS or OS (or both). Given that OS in the PROFILE 1014 trial is both immature and confounded by crossover, whereas PFS is much more mature and should not be affected by crossover, the ERG has focused its exploratory analysis on the remodelling of OS.

The ERG notes that the company's RPSFTM method of adjusting for the impact of treatment switching is flawed and that, as such, the company's crossover-adjusted HR is unreliable. The crossover-adjusted HR is not used to model OS in the first-line base case analysis, but the data that were used to calculate that HR are used as the basis of parametric curve estimates. Hence, the company's modelling of OS in the first-line model is also flawed.

Without access to the individual patient data from the PROFILE 1014 trial, the ERG is not able to investigate whether there are more appropriate ways to adjust the data for crossover. Instead, the ERG has investigated two scenarios for OS to try to establish a range of plausible ICERs per QALY gained. It is important to note that these scenarios do not represent absolute bounds for the upper and lower limits of OS gain for crizotinib – OS gain could, in reality, be greater or less than is presented in the ERG's scenarios. However, the ERG considers the two scenarios to be useful in establishing a logical range of possible estimates of OS gain in the absence of robust data.

The first scenario is that the pre-progression treatment effect for treatment with crizotinib carries on after progression, so that the benefit patients experience does not diminish with time i.e., the PFS treatment effect is the same as the PPS treatment effect. As noted in Section 5.6.3, there is some evidence to suggest that this is a plausible assumption. This assumption is implemented in the model by applying the PFS HR to the modelled crizotinib OS estimates. The ERG notes that the PH assumption does not hold for PFS in the PROFILE 1014 trial, so the results of this scenario should be treated with caution.

The second scenario assumes that there is no benefit to treatment with crizotinib after progression, or that the treatment effect falls to zero on progression i.e., PPS is equal for both treatments and any gain in OS is attributable only to better survival before progression. This scenario is implemented in the model by adjusting the exponential OS curve for treatment with pemetrexed so that PPS is equal to PPS for treatment with crizotinib.

In both ERG scenarios (Figure 12), the OS estimates for treatment with crizotinib used to estimate OS for treatment with pemetrexed are unadjusted for crossover. The ERG prefers to accept the level of crossover (19.2%) rather than use the company's RPSFTM-adjusted curve, as the company's RPSFTM-adjusted curve for treatment with crizotinib in the first-line model estimates better survival for crizotinib than the unadjusted curve. The ERG has not seen the details of the company's crossover methods and therefore cannot comment on the approach.

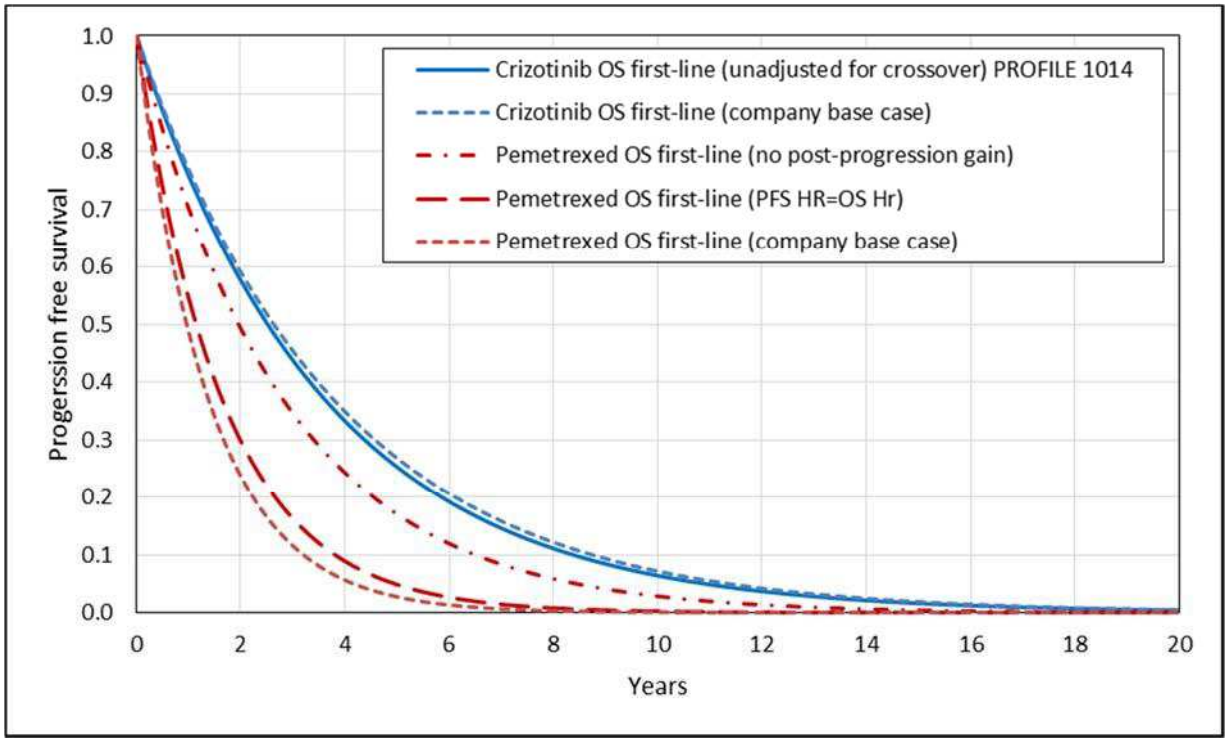


Figure 12 First-line OS: company base case and ERG scenarios (PROFILE 1014)

Source: company model; ERG calculations

Using the company's unadjusted modelling of OS in the first-line model and applying the PFS HR from the PROFILE 1014 trial to estimate OS for treatment with pemetrexed+platinum, the company's base case ICER per QALY gained increases by [redacted] to [redacted]. The company's base case ICER per QALY gained increases by [redacted] to [redacted] when equal PPS is assumed for both treatments.

Table 38 Cost effectiveness results of ERG exploratory OS modelling (first-line base case)

Modelling approach	Incremental cost	Incremental OS (months)	Incremental QALYs	ICER per QALY gained
Company base case (OS=RPSFT Wilcoxon)	[redacted]	28.70	1.28	[redacted]
Company model (OS=unadjusted for crossover)*	[redacted]	10.98	0.67	[redacted]

Scenario 1: OS treatment effect = PFS HR†	[redacted]	23.65	1.11	[redacted]
Scenario 2: OS treatment effect = no PPS gain†	[redacted]	9.55	0.62	[redacted]

OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year
Source: company model; ERG calculations
* this scenario removes the RPSFTM adjustment from both the crizotinib and pemetrexed+platinum OS estimates, which decreases incremental OS gain for crizotinib as a greater proportion of patients in the PROFILE 1014 trial switched from pemetrexed+platinum to crizotinib than from crizotinib to pemetrexed+platinum.
† these scenarios apply a treatment effect to crizotinib OS estimates (unadjusted for crossover) to estimate OS for pemetrexed+platinum.

Overall survival: subsequent-line treatment

The company has applied the PFS HR from the PROFILE 1007 trial to the RPSFTM-adjusted docetaxel OS curve in the subsequent-line base case analysis. The ERG is concerned that applying a HR to OS data that has already been adjusted for crossover somewhat defeats the point of trying to find a method that avoids the pitfalls of the RPSFTM approach.

The ERG has instead calculated the two OS scenarios (OS treatment effect=PFS HR and OS treatment effect=no PPS gain) as before but based on an exponential curve for treatment with crizotinib calculated from unadjusted OS estimates from the PROFILE 1007 trial (Figure 13). There is more substantial crossover from crizotinib to chemotherapy in the PROFILE 1007 trial than in the PROFILE 1014 trial; however, since patients are assumed to move to BSC once they stop treatment in the subsequent-line model, not adjusting for patients who receive further active treatment is an optimistic assumption for treatment with crizotinib.

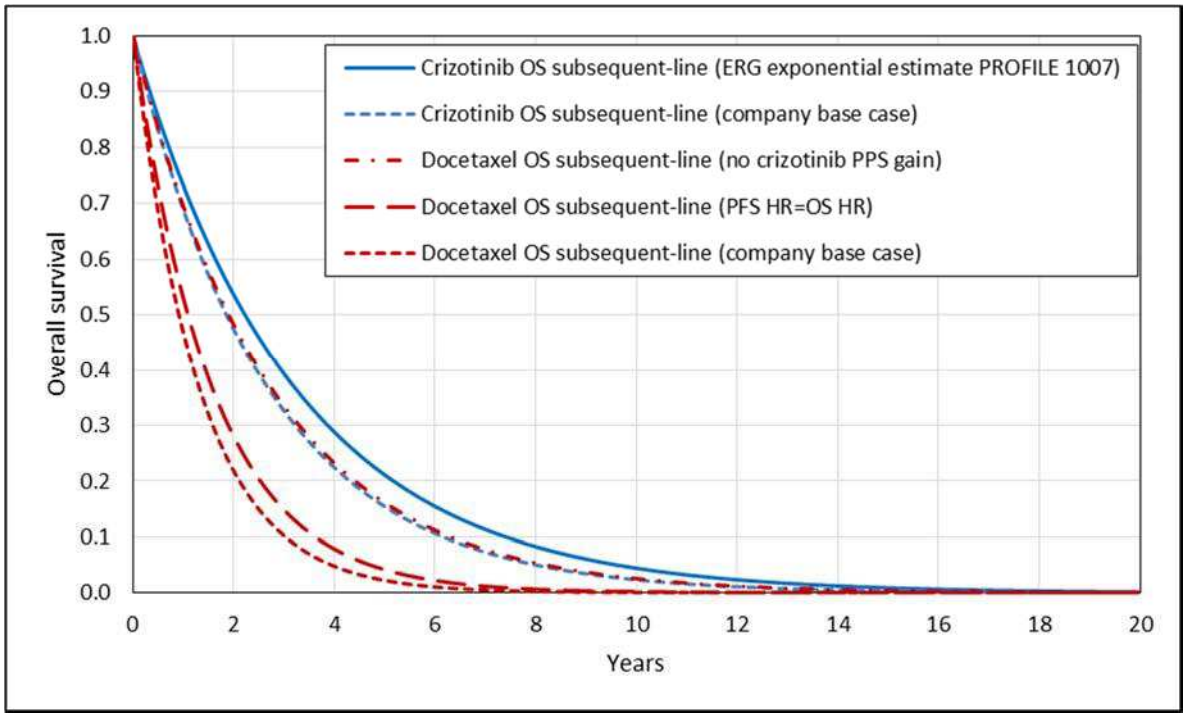


Figure 13 Subsequent-line OS: company base case and ERG scenarios (PROFILE 1007)

Source: company model; ERG calculations

Using unadjusted modelling of OS in the subsequent-line model and applying the PFS HR from the PROFILE 1007 trial to estimate OS for treatment with docetaxel, the base case ICER per QALY gained decreases by [redacted] to [redacted]. The base case ICER per QALY gained increases by [redacted] to [redacted] when equal PPS is assumed for both treatments.

Table 39 Cost effectiveness results of ERG exploratory OS modelling (subsequent-line base case)

Modelling approach	Incremental cost	Incremental OS (months)	Incremental QALYs	ICER per QALY gained
Company base case (OS=PFS HR based on RPSFT docetaxel estimate)	[redacted]	1.36	0.93	[redacted]
Scenario 1: OS treatment effect=PFS HR applied to unadjusted crizotinib	[redacted]	1.64	1.03	[redacted]
Scenario 2: OS treatment effect=no PPS gain	[redacted]	0.48	0.55	[redacted]

OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year
Source: company model; ERG calculations

PROFILE 1001 study scenario

The ERG does not consider the data from the PROFILE 1001 study to be sufficiently robust to provide reliable estimates of time-to-event outcomes for treatment with crizotinib in a ROS1+ advanced NSCLC population. The lack of a comparator arm in the PROFILE 1001 study is a particular concern, as it prevents robust conclusions about the comparative effectiveness of crizotinib in this population being drawn. Even if it were concluded that treatment with crizotinib results in different outcomes in a ROS1+ advanced NSCLC population versus an ALK+ advanced NSCLC population, it remains unknown whether patients receiving pemetrexed+platinum, docetaxel or any other treatment would also respond differently depending on whether they test positive for ROS1 or ALK rearrangements.

However, the ERG has remodelled the data from the PROFILE 1001 study in order to provide an alternative to the approach employed to by the company in its PROFILE 1001 scenario and investigate the sensitivity of the model to alternative assumptions. The ERG has explored the impact of different assumptions of treatment effect applied to the company's modelling of OS for treatment with crizotinib. It has also investigated the impact of modelling OS, PFS and TTD to improve face validity and to reduce mean OS.

Treatment effect

The company uses the RPSFTM (Wilcoxon)-adjusted HR from the PROFILE 1014 trial to estimate the treatment effect for OS for the ROS1+ advanced NSCLC population in the first-

line setting. The ERG has instead applied the same methods it applied to the updated OS data from the PROFILE 1014 trial: applying the PFS HR from the PROFILE 1014 trial to assume equal PPS for each treatment.

Applying the PFS HR from the PROFILE 1014 trial to the company's modelled OS estimates for treatment with crizotinib from the PROFILE 1001 study increases the ICER per QALY gained by [redacted] to [redacted] compared to the company's PROFILE 1001 scenario. Adjusting the OS curve for treatment with pemetrexed so that pemetrexed PPS equals crizotinib PPS increases the ICER per QALY gained by [redacted] to [redacted] compared to the company's PROFILE 1001 scenario.

The company has already used the PFS HR from the PROFILE 1014 trial to estimate PFS treatment effect for the PROFILE 1001 scenario, so the ERG has made no change to the modelling of PFS. The ERG has also made no change to the modelling of TTD, since the data are almost complete.

The company uses the PFS HR from the PROFILE 1007 trial in its PROFILE 1001 scenario for subsequent-line treatment. This yields an ICER per QALY gained of [redacted]. The ERG has also investigated the effect of assuming equal PPS for treatment with docetaxel and crizotinib, which represents the assumption that treatment effect falls to zero immediately on progression. Adjusting the OS curve for treatment with docetaxel so that docetaxel PPS equals crizotinib PPS increases the ICER per QALY gained by [redacted] to [redacted] compared to the company's PROFILE 1001 scenario.

The ERG has made no change to the modelling of PFS or TTD in the subsequent-line PROFILE 1001 scenario.

Crizotinib time-to-event estimates

The ERG has investigated the impact of remodelling OS, PFS and TTD from the PROFILE 1001 study by using 'all-lines' K-M data directly as far as possible and then appending an exponential tail to project out to the time horizon (Figure 14). Details of this method are given in Appendix 10.5. This method relies on the assumption that survival has settled into a long-term trend that is apparent in the data. However, the ERG cautions that, given the small size of the study and the immaturity of the data in the PROFILE 1001 study, this assumption is unlikely to hold for OS in particular. The cost effectiveness results based on any modelling of time-to-event data from the PROFILE 1001 study are subject to substantial uncertainty.

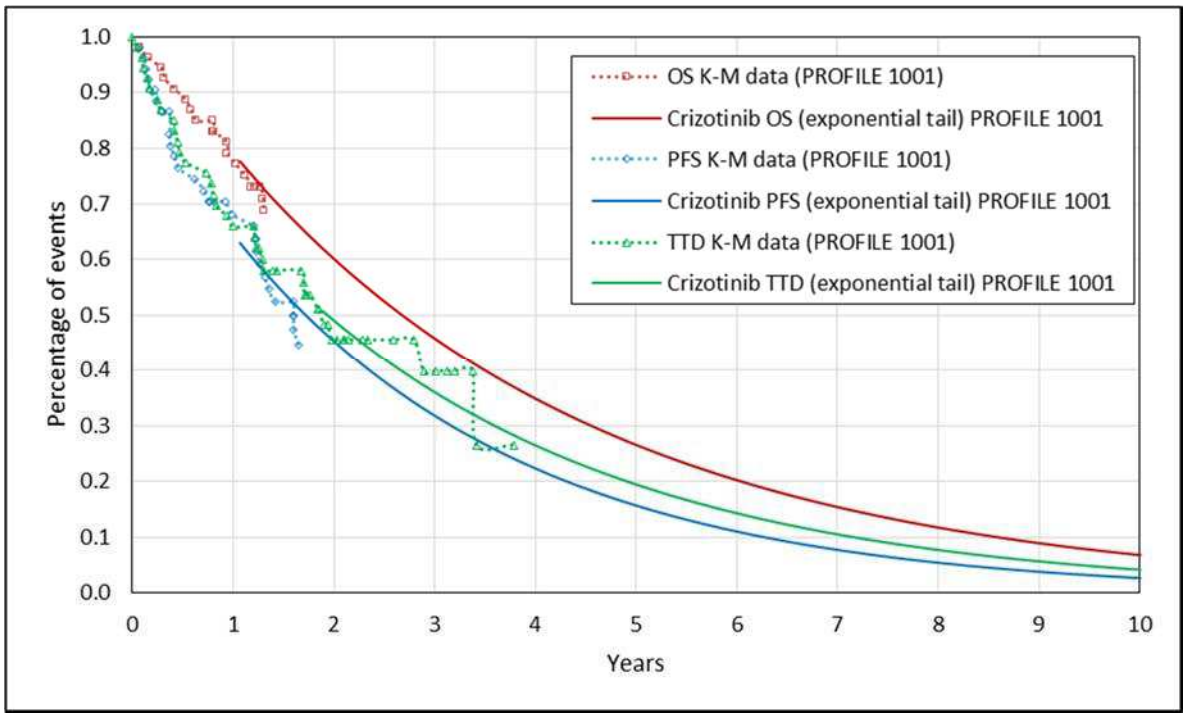


Figure 14 PROFILE 1001 'all-lines' ERG model: K-M data+exponential tail

Source: clarification B1; ERG calculations

Mean OS for treatment with crizotinib (first- and subsequent-line) is reduced from 69 months (5.8 years) in the company PROFILE 1001 scenario to 45.7 months (3.8 years) in the ERG model (Figure 15). Mean PFS for treatment with crizotinib (first- and subsequent-line) is reduced from 34.3 months (2.9 years) in the company scenario to 31.8 months (2.7 years) in the ERG model. Mean TTD for treatment with crizotinib (first- and subsequent-line) increases slightly from 35.7 months to 36.9 months, so mean time on treatment after progression is increased from 1.9 months to 5.1 months.

The ERG has estimated the treatment effect for OS and PFS in this scenario by applying the PFS HR from the 1014 trial in the first-line (Figure 15, Figure 16) and by applying the PFS HR from the 1007 trial in the subsequent-line (Figure 17 and Figure 18) to the 'all-lines' K-M data+exponential crizotinib model. The ERG has not amended TTD for pemetrexed+platinum and docetaxel in this scenario.

Mean OS gain for treatment with crizotinib versus pemetrexed in the first-line setting is reduced to 23.8 months (2.0 years) in the ERG PROFILE 1001 study scenario versus 43 months (3.6 years) in the company scenario. Mean PFS gain is reduced slightly from 18.2 months (1.5 years) in the company PROFILE 1001 study scenario to 17.4 months in the ERG scenario.

Compared to the company's PROFILE 1001 scenario first-line ICER, applying the ERG's remodelled PROFILE 1001 study data in the first-line setting increases the ICER per QALY gained by [redacted] to [redacted].

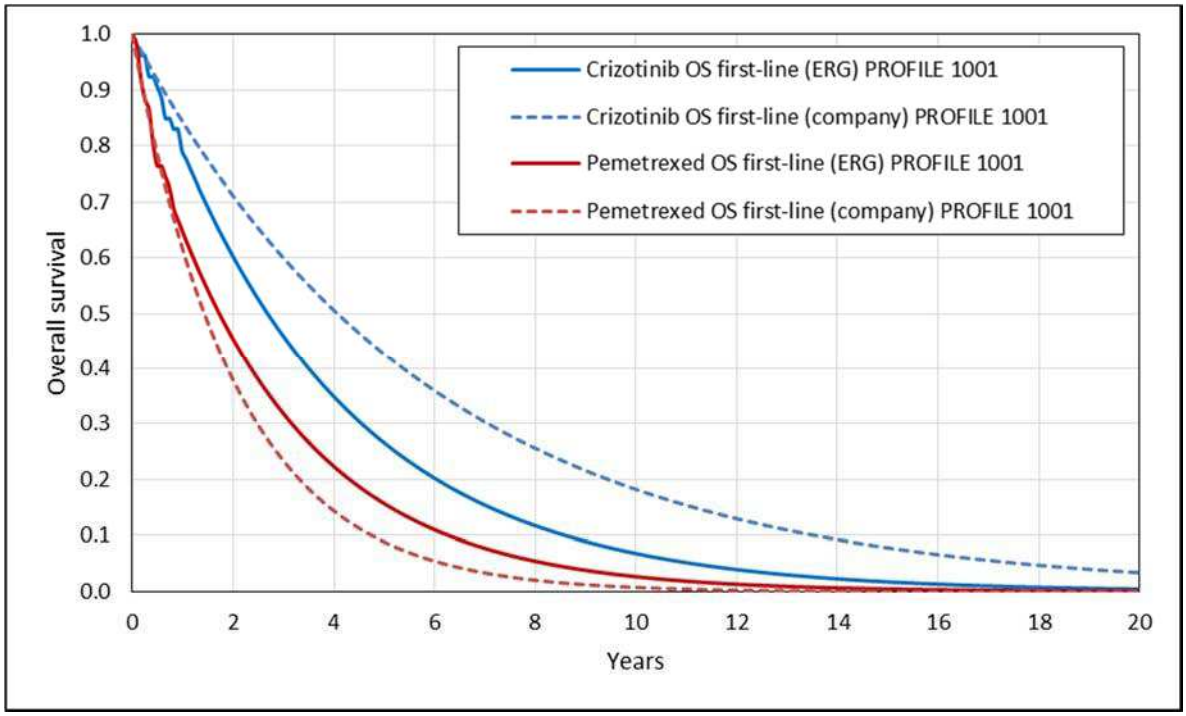


Figure 15 First-line OS (PROFILE 1001): company model versus ERG model

Source: company model; ERG calculations

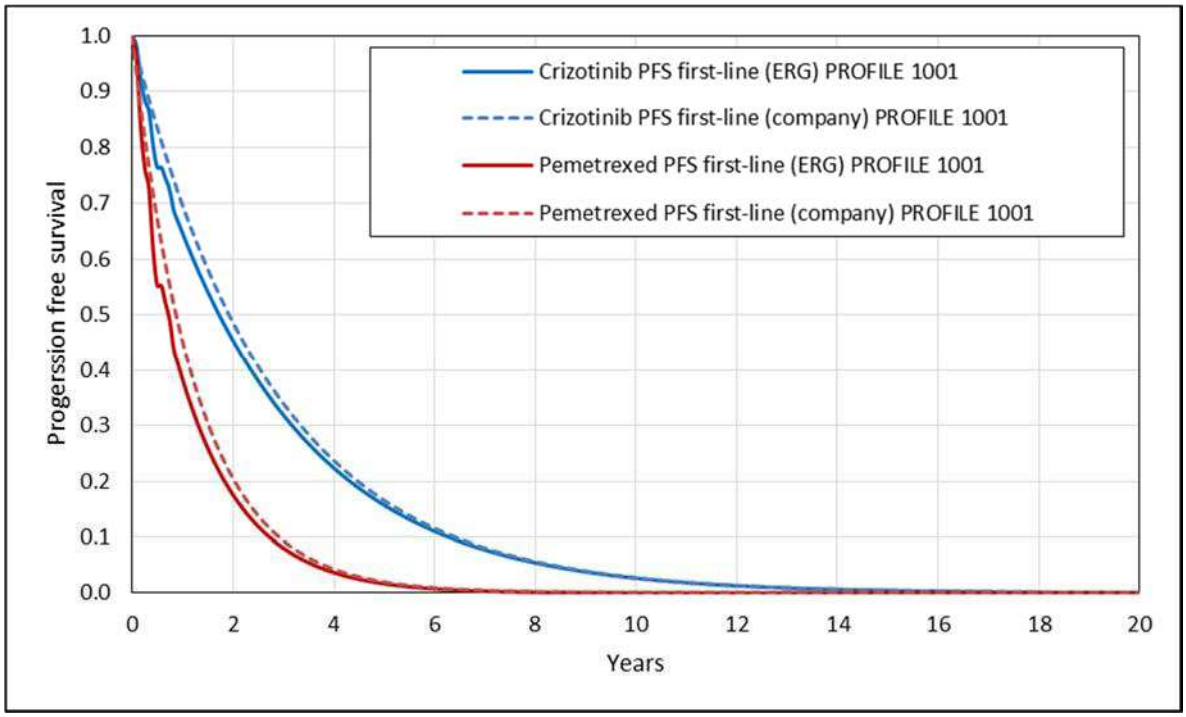


Figure 16 First-line PFS (PROFILE 1001): company model versus ERG model

Source: company model; ERG calculations

Mean OS gain for treatment with crizotinib versus docetaxel in the subsequent-line is reduced to 22.3 months (1.9 years) in the ERG PROFILE 1001 study scenario versus 41.1 months (3.4 years) in the company scenario. Mean PFS gain is reduced slightly from 17.1 months (1.4 years) in the company PROFILE 1001 study scenario to 16.3 months in the ERG scenario.

Compared to the company's PROFILE 1001 scenario subsequent-line ICER, applying the ERG's remodelled PROFILE 1001 study data in the subsequent-line model increases the ICER per QALY gained by [redacted] to [redacted].

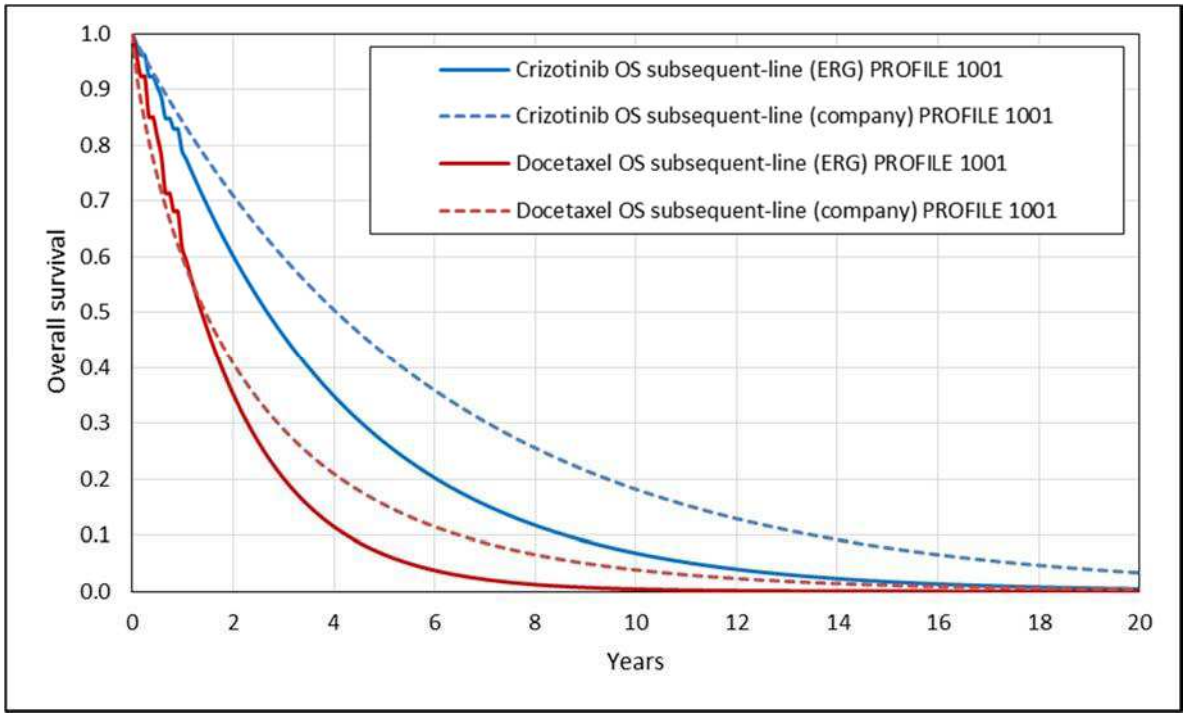


Figure 17 Subsequent-line OS (PROFILE 1001): company model versus ERG model

Source: company model; ERG calculations

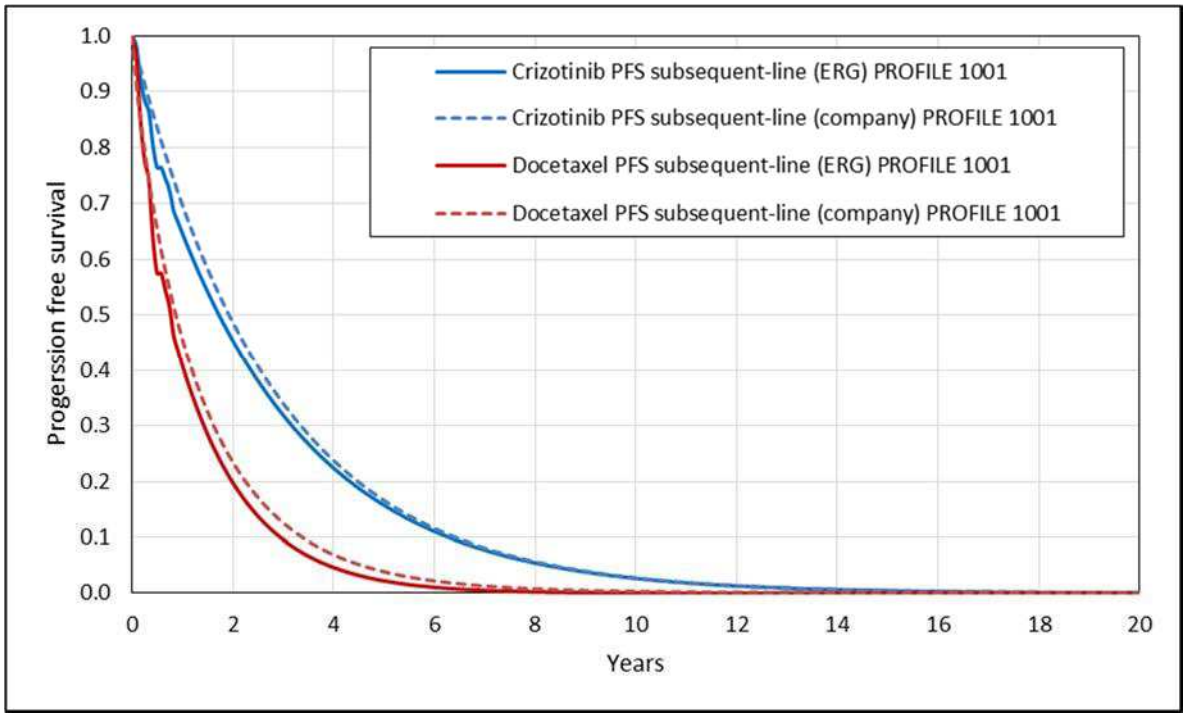


Figure 18 Subsequent-line PFS (PROFILE 1001): company model versus ERG model

Source: company model; ERG calculations

Progression-free utility values: first-line treatment

Given the lack of long-term EQ-5D data for treatment with pemetrexed+platinum, the lack of a statistically significant difference between mean EQ-5D estimates for those cycles where data have been recorded and the potential influence of the open-label nature of the trial on patients' responses to the EQ-5D, the ERG has explored the impact of assuming that there is no difference in PFS utility values between treatment with crizotinib and treatment with pemetrexed+platinum. The ERG has also explored the impact of using a PFS utility value of 0.75 for treatment with pemetrexed+platinum. These analyses do not resolve the company's inconsistent use of data i.e., use of adjusted baseline characteristics for the time-to-event estimates and use of unadjusted utility values.

If the PFS utility in both arms is assumed to be the same as the base case crizotinib PFS utility (0.81), the first-line base case ICER increases by [redacted] to [redacted] per QALY gained. If the PFS utility in both arms is assumed to be the same as the base case pemetrexed+platinum PFS utility (0.72), the first-line base case ICER increases by [redacted] to [redacted] per QALY gained. If the PFS utility for treatment with pemetrexed+platinum is assumed to be 0.75, the first-line base case ICER increases by [redacted] to [redacted] per QALY gained.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG has made the following revisions to the company base case ICERs for treatment with crizotinib versus pemetrexed+platinum in the first-line setting and treatment with crizotinib versus docetaxel in the subsequent-line setting:

First-line treatment

Base case survival estimates:

- ERG OS treatment effect: use PFS HR from PROFILE 1014 trial [R1a]
- ERG OS treatment effect: no PPS gain [R1b]

PROFILE 1001 scenario survival estimates:

- ERG OS treatment effect: use PFS HR from PROFILE 1014 [R2a]
- ERG OS treatment effect: no PPS gain [R2b]
- ERG remodel crizotinib time-to-event: K-M data+exponential [R3]

PFS utility values:

- ERG PFS utility: crizotinib utility (0.81) for both treatments [R7a]
- ERG PFS utility: pemetrexed utility (0.72) for both treatments [R7b]
- ERG PFS utility: pemetrexed utility = 0.75 [R7c]

Subsequent-line treatment

Base case survival estimates:

- ERG OS treatment effect: apply PFS HR from PROFILE 1007 to unadjusted crizotinib estimate) [R4a]
- ERG OS treatment effect: no PPS gain [R4b]

PROFILE 1001 scenario survival estimates:

- ERG OS treatment effect: no PPS gain [R5]
- ERG remodel crizotinib time-to-event: K-M data+exponential [R6]

The ERG notes that the company's subsequent-line PROFILE 1001 analysis applies the PFS HR from the PROFILE 1007 trial to modelled crizotinib OS from the PROFILE 1001 study. The ERG has therefore not modelled the application of the PFS HR from the PROFILE 1007 trial as an exploratory scenario in the subsequent-line PROFILE 1001 analysis.

In both the first- and subsequent-line models, the ERG has only included changes that have a substantial impact on the size of the estimated ICER per QALY gained and has not included the effects of minor issues (Section 5.6.4).

In both the first- and subsequent-line models, the ERG has only included changes that have a substantial impact on the size of the estimated ICER per QALY gained and has not included the effects of minor issues (Section 5.6.4).

A summary of the individual effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of treatment with crizotinib versus pemetrexed+platinum in the first-line setting is shown in **Error! Reference source not found.**. A summary of the individual effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of treatment with crizotinib versus docetaxel in the subsequent-line setting is given in Table 42.

A summary of the individual effects of the ERG's model amendments on the company's PROFILE 1001 cost effectiveness results for the comparison of treatment with crizotinib versus pemetrexed+platinum in the first-line setting is given in Table 43. A summary of the individual effects of the ERG's model amendments on the company's PROFILE 1001 cost effectiveness results for the comparison of treatment with crizotinib versus docetaxel in the subsequent-line setting is shown in Table 45.

Given the fundamental uncertainties in this appraisal (Section 5.6.1), the ERG is not able to provide preferred base case ICERs per QALY gained. The ERG has instead provided a number of scenario combinations that explore the sensitivity of the company's models to alternative methods of estimating OS and utility values for PFS. These scenarios are shown in **Error! Reference source not found.** and Table 44 for the first-line model.

Table 40 Base case cost effectiveness results for crizotinib (PAS) versus pemetrexed (first-line): ERG revisions

ERG revisions	Crizotinib			Pemetrexed			Incremental			ICER
	Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company updated base case (from 24 November 2017)	[redacted]	3.86	2.13	£23,267	1.47	0.84	[redacted]	2.39	1.28	[redacted]
R1a) OS treatment effect: use PFS HR from 1014	[redacted]	3.70	2.06	£23,777	1.73	0.96	[redacted]	1.97	1.11	[redacted]
R1b) OS treatment effect: no PPS gain	[redacted]	3.70	2.06	£25,848	2.91	1.44	[redacted]	0.80	0.62	[redacted]
R7a) PFS utility: crizotinib utility (0.81) for both*	[redacted]	3.86	2.13	£23,267	1.47	0.90	[redacted]	2.39	1.23	[redacted]
R7b) PFS utility: pemetrexed utility (0.72) for both*	[redacted]	3.86	2.00	£23,267	1.47	0.84	[redacted]	2.39	1.15	[redacted]
R7c) PFS utility: pemetrexed utility = 0.75*	[redacted]	3.86	2.13	£23,267	1.47	0.86	[redacted]	2.39	1.26	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year

*When applied individually, PFS utility scenarios should be applied to the company base case model including the company's modelling of OS (adjusted for crossover using RPSFTM Wilcoxon)

Table 41 Base case cost effectiveness results for crizotinib (PAS) versus pemetrexed (first-line): ERG scenarios

Model scenarios			Crizotinib			Pemetrexed			Incremental			ICER
			Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company updated base case (from 24 November 2017)			[redacted]	3.86	2.13	£23,267	1.47	0.84	[redacted]	2.39	1.28	[redacted]
R1a, R7a	OS treatment effect: use PFS HR from 1014	PFS utility=0.81 for both	[redacted]	3.70	2.06	£23,777	1.73	1.01	[redacted]	1.97	1.05	[redacted]
R1a, R7b		PFS utility=0.72 for both	[redacted]	3.70	1.94	£23,777	1.73	0.96	[redacted]	1.97	0.98	[redacted]
R1a, R7c		PFS utility=0.75 for pemetrexed	[redacted]	3.70	2.06	£23,777	1.73	0.98	[redacted]	1.97	1.09	[redacted]
R1b, R7a	OS treatment effect: no PPS gain	PFS utility=0.81 for both	[redacted]	3.70	2.06	£25,848	2.91	1.50	[redacted]	0.80	0.57	[redacted]
R1b, R7b		PFS utility=0.72 for both	[redacted]	3.70	1.94	£25,848	2.91	1.44	[redacted]	0.80	0.49	[redacted]
R1b, R7c		PFS utility=0.75 for pemetrexed	[redacted]	3.70	2.06	£25,848	2.91	1.46	[redacted]	0.80	0.60	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year

Table 42 Base case cost effectiveness results for crizotinib (PAS) versus docetaxel (subsequent-line): ERG revisions

Model scenario and ERG revisions	Crizotinib			Docetaxel			Incremental			ICER
	Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company base case	[redacted]	**2.75**	**1.63**	**£11,076**	**1.39**	**0.71**	[redacted]	**1.36**	**0.93**	[redacted]
R4a) OS treatment effect: apply PFS HR to unadjusted crizotinib estimate	[redacted]	3.29	1.84	£11,520	1.65	0.82	[redacted]	1.64	1.03	[redacted]
R4b) OS treatment effect: no PPS treatment effect	[redacted]	3.29	1.84	£13,428	2.81	1.29	[redacted]	0.48	0.55	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression free survival; PPS=post-progression survival; QALY=quality adjusted life year

Table 43 PROFILE 1001 scenario cost effectiveness results for crizotinib (PAS) versus pemetrexed (first-line): ERG revisions

ERG revisions	Crizotinib			Pemetrexed			Incremental			ICER
	Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company PROFILE 1001 scenario	[redacted]	**5.75**	**3.25**	**£22,570**	**2.15**	**1.29**	[redacted]	**3.60**	**1.95**	[redacted]
R2a) OS treatment effect: use PFS HR from 1014	[redacted]	5.75	3.25	£23,662	2.74	1.54	[redacted]	3.01	1.71	[redacted]
R2b) OS treatment effect: no PPS gain	[redacted]	5.75	3.25	£26,110	4.24	2.11	[redacted]	1.52	1.13	[redacted]
R3) Remodel crizotinib time-to-event: K-M data+ exponential	[redacted]	3.81	2.56	£21,979	1.83	1.13	[redacted]	1.98	1.43	[redacted]
R7a) PFS utility: crizotinib utility (0.81) for both	[redacted]	5.75	3.25	£22,570	2.15	1.41	[redacted]	3.60	1.84	[redacted]
R7b) PFS utility: pemetrexed utility (0.72) for both	[redacted]	5.75	3.00	£22,570	2.15	1.29	[redacted]	3.60	1.70	[redacted]
R7c) PFS utility: pemetrexed utility = 0.75	[redacted]	5.75	3.25	£22,570	2.15	1.33	[redacted]	3.60	1.91	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year

Table 44 PROFILE 1001 cost effectiveness results for crizotinib (PAS) versus pemetrexed (first-line): ERG scenarios

Model scenarios			Crizotinib			Pemetrexed			Incremental			ICER
			Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company PROFILE 1001 scenario			[redacted]	**5.75**	**3.25**	**£22,570**	**2.15**	**1.29**	[redacted]	**3.60**	**1.95**	[redacted]
R2a, R7a	OS treatment effect: use PFS HR from 1014	PFS utility=0.81 for both	[redacted]	5.75	3.25	£23,662	2.74	1.65	[redacted]	3.01	1.59	[redacted]
R2a, R7b		PFS utility=0.72 for both	[redacted]	5.75	3.00	£23,662	2.74	1.54	[redacted]	3.01	1.46	[redacted]
R2a, R7c		PFS utility=0.75 for pemetrexed	[redacted]	5.75	3.25	£23,662	2.74	1.58	[redacted]	3.01	1.67	[redacted]
R2b, R7a	OS treatment effect: no PPS gain	PFS utility=0.81 for both	[redacted]	5.75	3.25	£26,110	4.24	2.23	[redacted]	1.52	1.02	[redacted]
R2b, R7b		PFS utility=0.72 for both	[redacted]	5.75	3.00	£26,110	4.24	2.11	[redacted]	1.52	0.89	[redacted]
R2b, R7c		PFS utility=0.75 for pemetrexed	[redacted]	5.75	3.25	£26,110	4.24	2.15	[redacted]	1.51	1.09	[redacted]
R3, R7a	Remodel crizotinib time-to-event: K-M data+ exponential	PFS utility=0.81 for both	[redacted]	3.81	2.56	£21,979	1.83	1.24	[redacted]	1.98	1.33	[redacted]
R3, R7b		PFS utility=0.72 for both	[redacted]	3.81	2.31	£21,979	1.83	1.13	[redacted]	1.98	1.18	[redacted]
R3, R7c		PFS utility=0.75 for pemetrexed	[redacted]	3.81	2.56	£21,979	1.83	1.17	[redacted]	1.98	1.40	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life year

Table 45 PROFILE 1001 scenario cost effectiveness results for crizotinib (PAS) versus docetaxel (subsequent-line): ERG revisions

ERG revisions	Crizotinib			Docetaxel			Incremental			ICER
	Cost	LYG	QALYs	Cost	LYG	QALYs	Cost	LYG	QALYs	£/QALY
Company PROFILE 1001 scenario*	[redacted]	**5.75**	**3.24**	**£12,706**	**2.32**	**1.29**	[redacted]	**3.43**	**1.95**	[redacted]
R5) OS treatment effect: no PPS gain	[redacted]	5.75	3.24	£15,606	4.24	2.03	[redacted]	1.51	1.21	[redacted]
R6) Remodel crizotinib time-to-event: K-M data+ exponential	[redacted]	3.81	2.55	£12,080	1.95	1.11	[redacted]	1.86	1.45	[redacted]

ERG=Evidence Review Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; LYG=life years gained; OS=overall survival; PFS=progression free survival; PPS=post-progression survival; QALY=quality adjusted life year

*Please note: the company PROFILE 1001 study scenario represents PFS HR from PROFILE 1007 to PROFILE 1001 data

6.1 Conclusions of the cost effectiveness section

The various revisions implemented by the ERG in the company models for the comparison of treatment with crizotinib versus pemetrexed+platinum in the first-line setting and crizotinib versus docetaxel in the subsequent-line setting yield a mixture of effects. Incremental costs and incremental benefits both increase and decrease depending on the individual revision or combination of revisions (scenarios).

The resulting ICERs per QALY gained in the first-line base case vary from [redacted] (using pemetrexed+platinum PFS utility of 0.75) to [redacted] (assuming no PPS treatment effect and a PFS utility of 0.72 for both treatments). The resulting ICERs per QALY gained in the subsequent-line base case vary from [redacted] (docetaxel OS=applying PFS HR to unadjusted crizotinib OS estimates) to [redacted] (assuming no PPS treatment effect).

The resulting ICERs per QALY gained in the first-line PROFILE 1001 scenario vary from [redacted] (using pemetrexed+platinum PFS utility of 0.75) to [redacted] (assuming no PPS treatment effect and a PFS utility of 0.72 for both treatments). The resulting ICERs per QALY gained in the subsequent-line PROFILE 1001 scenario vary from [redacted] (remodel crizotinib time-to-event: K-M data+ exponential) to [redacted] (assuming no PPS treatment effect).

7 END OF LIFE

The NICE End of Life criteria, and the data presented by the company to show that these criteria have been met, are presented in Table 46.

Table 46 Company summary of evidence for End of Life consideration

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	There is a paucity of estimates of OS with current chemotherapy in the ROS1+ advanced NSCLC population specifically. There is no conclusive evidence that ROS1-positivity is a better prognostic factor for survival, compared to unselected NSCLC. Based on opinion from 12 leading clinical experts from the UK, the PFS in chemotherapy-treated ROS1+ patients is similar to the PFS in chemotherapy-treated ALK+ patients. As there are limited data on OS for ROS1+ advanced NSCLC patients, data from ALK+ NSCLC have been used as supportive evidence, due to the similarities between patients with ALK and ROS1. Estimates for median OS in ALK+ patients range from 6 to 22 months, with median OS in the chemotherapy arm of PROFILE 1007 reaching 21.9 months at the final analysis. Based on the available evidence and support from 12 UK leading clinical experts, the life expectancy of ROS1+ advanced NSCLC patients is expected to be less than 24 months
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median OS was not reached in PROFILE 1001, with only 30.2% of patients having died at the time of PFS analysis (30th November 2014). At this point, median PFS was 19.3 months, therefore this is expected to be the minimum value for OS. In the previous appraisal of crizotinib as a subsequent-line therapy for ALK+ NSCLC, it was acknowledged that PFS is considered a conservative indicator of OS for targeted therapies: *"[The Committee] discussed comments by the manufacturer that it is biologically plausible that the overall survival to PFS ratio would be higher with targeted therapy than with chemotherapy. The clinical specialists confirmed that in some patients there was a dramatic response to treatment and that targeted therapies such as crizotinib could reduce tumour size to below that at the beginning of therapy. Therefore, at progression, the size of the tumour could still be smaller than at the beginning of therapy and as a result, benefit would continue into the progressed disease stage. The Committee was persuaded by this evidence."*[99] Crizotinib demonstrated clear benefits in terms of tumour response in PROFILE 1001, which, based on the NICE Committee's previous considerations, is supportive of a continued survival benefit with crizotinib into progressed disease. As such, the observed PFS with crizotinib should be considered an absolute minimum estimate of OS. In both the first-line and the subsequent-line settings, NICE has accepted an extension of life of more than three months in ALK+ advanced NSCLC patients receiving crizotinib compared to standard care. The model predicts an extension to life associated with crizotinib in ROS1+ patients of 2.39 years compared to pemetrexed plus platinum therapy and 1.36 years compared to docetaxel therapy, which therefore meets the NICE criteria for end-of-life.

Source: CS, Table 25

7.1 Short life expectancy

The evidence for life expectancy in the ROS1+ advanced NSCLC population is uncertain, particularly given the lack of comparator data available from the PROFILE 1001 study.

The Appraisal Committee in TA406 considered that life expectancy in the ALK+ advanced NSCLC population in the first-line setting was likely to be less than 24 months and that the short life expectancy criterion was met. This consideration was made taking into account the company's revised model that used an earlier data cut from the PROFILE 1014 trial than is used in this appraisal. This consideration was made based on estimates of OS with adjusted baseline characteristics.

The Appraisal Committee in TA422 noted that there was some uncertainty around life expectancy in the ALK+ advanced NSCLC population in the subsequent-line setting, but considered that, on balance, it was likely to be less than 24 months and that the short life expectancy criterion was met.

7.2 Extension to life

The evidence for extension to life in the ROS1+ advanced NSCLC population is uncertain, particularly given the lack of a comparator to crizotinib in the PROFILE 1001 study.

The Appraisal Committee in TA406 considered that it could be sufficiently confident that treatment with crizotinib in the first-line setting would offer at least 3 months of additional survival benefit in the ALK+ advanced NSCLC population, although the size of the OS benefit was unclear. It concluded that the extension to life criterion was met.

The Appraisal Committee in TA422 considered that treatment with crizotinib in the subsequent-line setting would offer at least 3 months of additional survival benefit in the ALK+ advanced NSCLC population. The Appraisal Committee concluded that the extension to life criterion was met. However, the ERG notes that the NHS standard of care for this group of patients has recently changed and is now docetaxel+nintedanib (which has not been included as a comparator in this appraisal).

8 OVERALL CONCLUSIONS

8.1 Clinical effectiveness

The ERG considers that the company has addressed the decision problem **only** if it is considered that outcome data from patients with ALK+ advanced NSCLC can be used as a proxy for the outcome data of patients with ROS1+ advanced NSCLC. The ERG considers that the evidence (PROFILE 1001 study, PROFILE 1007 and PROFILE 1014 trials) presented by the company was generally of good quality. The ERG notes that the OS data available for patients treated with ROS1+ advanced NSCLC or patients with ALK+ advanced NSCLC are immature.

8.2 Cost effectiveness

The company base case analysis is founded on the assumption that the outcomes of treatment with crizotinib in an ALK+ advanced NSCLC population are an appropriate proxy for the outcomes of treatment with crizotinib in a ROS1+ advanced NSCLC population. The scenario analysis for the ROS1+ advanced NSCLC population is based on a small, immature, single-arm study (PROFILE 1001) and any modelling of this data will likely be subject to substantial uncertainty.

The ERG's revised ICERs per QALY gained vary greatly depending on which of its revisions are taken into account. The ICERs per QALY gained for treatment with crizotinib versus pemetrexed+platinum in the first-line base case vary from [redacted] to [redacted]. The ICERs per QALY gained for treatment with crizotinib versus docetaxel in the subsequent-line base case vary from [redacted] to [redacted]. The ICERs per QALY gained for treatment with crizotinib versus pemetrexed+platinum in the first-line PROFILE 1001 scenario vary from [redacted] to [redacted]. The ICERs per QALY gained for treatment with crizotinib versus docetaxel in the subsequent-line PROFILE 1001 scenario vary from [redacted] to [redacted].

8.3 Implications for research

There are currently no comparative studies evaluating the use of crizotinib in ROS1+ advanced NSCLC patients and it is unlikely that such studies will become available due to the perceived lack of clinical equipoise and the small number of patients with ROS1+ advanced NSCLC. An international, multicentre, prospective single-arm cohort study with appropriate long duration of follow-up could shed more light on the effectiveness of crizotinib and particularly the impact of crizotinib on the OS of patients with ROS1+ advanced NSCLC. An international registry would be a useful alternative for collecting data on this patient population.

9 REFERENCES

1. Cancer Research UK. The twenty most common cancers (UK 2014). 2014; Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Zero. [Accessed October 2017].
2. Royal College of Physicians. National Lung Cancer Audit Annual Report 2016: for the audit period 2015. 2017. Available from: https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2016. [Accessed October 2017].
3. Sulu E, Tasolar O, Berk Takir H, Yagci Tuncer L, Karakurt Z, Yilmaz A. Delays in the diagnosis and treatment of non-small-cell lung cancer. Tumori. 2011; 97:693-7.
4. Cancer Research UK. Lung cancer (C33-C34), proportion of cases diagnosed at each stage. Available from: http://www.cancerresearchuk.org/sites/default/files/cstream-node/inc_by_stage_country_lung.xls. [Accessed October 2017].
5. Cancer Research UK. Lung cancer survival. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Two [Accessed October 2017].
6. Clinical Lung Cancer Genome Project and Network Genomic Medicine. A genomics-based classification of human lung tumors. Sci Transl Med. 2013; 5:209, ra153.
7. Bergethon K, Shaw AT, Ou SH, Katayama R, Lovly CM, McDonald NT*, et al.* ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol. 2012; 30: 863-70.
8. Clavé S, Gimeno J, Muñoz-Mármol AM, Vidal J, Reguart N, Carcereny E*, et al.* ROS1 copy number alterations are frequent in non-small cell lung cancer. Oncotarget. 2016; 7: 8019-28.
9. Scheffler M, Schultheis A, Teixido C, Michels S, Morales-Espinosa D, Viteri S*, et al.* ROS1 rearrangements in lung adenocarcinoma: prognostic impact, therapeutic options and genetic variability. Oncotarget. 2015; 6: 10577-85.
10. Mazieres J, Zalcman G, Crino L, Biondani P, Barlesi F, Filleron T*, et al.* Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. J Clin Oncol. 2015; 33: 992-9.
11. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H*, et al.* Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell. 2007; 131: 1190-203.
12. Uguen A, De Braekeleer M. ROS1 fusions in cancer: a review. Future Oncol. 2016; 12:1911-28.
13. Shaw AT, Ou S-HI, Bang Y-J, Camidge DR, Solomon BJ, Salgia R*, et al.* Crizotinib in ROS1-rearranged non–small-cell lung cancer. N Engl J Med. 2014; 371: 1963-71.
14. European Medicines Agency (EMA). Xalkori: European Public Assessment Report [EPAR] 2016; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002489/WC500213275.pdf [Accessed October 2017].
15. National Institute for Health and Care Excellence (NICE). Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer: Guidance [TA406]. Available from: https://www.nice.org.uk/guidance/ta406 Last Accessed 06 October 2017.
16. Takeuchi K, Soda M, Togashi Y, Suzuki R, Sakata S, Hatano S*, et al.* RET, ROS1 and ALK fusions in lung cancer. Nat Med. 2012; 18: 378-81.
17. Acquaviva J, Wong R, Charest A. The multifaceted roles of the receptor tyrosine kinase ROS in development and cancer. Biochimica et biophysica acta. 2009; 1795: 37-52.
18. Facchinetti F, Rossi G, Bria E, Soria JC, Besse B, Minari R*, et al.* Oncogene addiction in non-small cell lung cancer: Focus on ROS1 inhibition. Cancer Treat Rev. 2017; 55:83-95.

19. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S*, et al.* Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007; 448: 561-6.
20. Huber KV, Salah E, Radic B, Gridling M, Elkins JM, Stukalov A*, et al.* Stereospecific targeting of MTH1 by (S)-crizotinib as an anticancer strategy. Nature. 2014; 508: 222-7.
21. Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. Oncologist. 2013; 18: 865-75.
22. Pfizer Ltd. Data on file - clinical advisory board with 12 UK leading clinical experts 5th July 2017.
23. Pfizer Ltd. PROFILE 1007: Statistical Analysis Plan. 2012.
24. Pfizer Ltd. PROFILE 1007: Clinical protocol. 2014.
25. Pfizer Ltd. PROFILE 1007: Interim Clinical Study Report. 2015.
26. Pfizer Ltd. PROFILE 1007 Clinical Study Report: ID1098. 2016.
27. Pfizer Ltd. PROFILE 1007 Clinical Study Report: Updated OS Results. 2017.
28. Solomon BJ, Mok T, Kim D-W, Wu Y-L, Nakagawa K, Mekhail T*, et al.* First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014a; 371: 2167-77.
29. European Medicines Agency (EMA). Xalkori: European Public Assessment Report [EPAR]. 2012.; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002489/WC500134761.pdf [accessed October 2017].
30. National Institute for Health and Care Excellence (NICE). Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [TA422]. 2016; Available from: https://www.nice.org.uk/guidance/ta422 [Accessed October 2017].
31. Pfizer Ltd. PROFILE 1014: Statistical Analysis Plan. 2014.
32. Pfizer Ltd. PROFILE 1014: Clinical protocol. 2015.
33. Pfizer Ltd. PROFILE 1014: Clinical Study Report. 2015.
34. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ*, et al.* Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013; 368: 2385-94.
35. European Medicines Agency (EMA). Xalkori: European Public Assessment Report [EPAR] 2015; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002489/WC500200132.pdf [Accessed October 2017].
36. National Institute for Health and Care Excellence (NICE). Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [TA406]. 2016; Available from: https://www.nice.org.uk/guidance/ta406/documents/committee-papers-2 [Accessed October 2017].
37. The British Thoracic Oncology Group, The National Cancer Research Institute, The Royal College of Physicians, The Association of Cancer Physicians. Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer [ID1098]. Clinical Expert Statement. 2017.
38. Pfizer Ltd. PROFILE 1001: Clinical protocol. 2014.
39. Pfizer Ltd. PROFILE 1001: Statistical Analysis Plan. 2014.
40. Pfizer Ltd. PROFILE 1001: Supplemental Statistical Analysis Plan. 2015.
41. Pfizer Ltd. PROFILE 1001: Clinical Study Report. 2016.
42. Shaw A, Riely G, Bang Yea. Crizotinib in advanced ROS1-rearranged non-small cell lung cancer (NSCLC): updated results from PROFILE 1001. ESMO Congress (2016). 2016a; Poster 1206PD.
43. National Institute for Health and Care Excellence (NICE). Lung cancer: the diagnosis and treatment of lung cancer [CG121]. 2011; Available from:

https://www.nice.org.uk/guidance/cg121/chapter/1-Guidance#treatment. [Accessed October 2017].
44. National Institute for Health and Care Excellence (NICE). Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy [TA374]. 2015; Available from: https://www.nice.org.uk/guidance/ta374/history. [Accessed October 2017].
45. National Institute for Health and Care Excellence (NICE). Pemetrexed for the first-line treatment of non-small-cell lung cancer [TA181]. 2009; Available from: https://www.nice.org.uk/guidance/ta181. [Accessed October 2017].
46. National Institute for Health and Care Excellence (NICE). Pemetrexed for the maintenance treatment of non-small-cell lung cancer [TA190]. 2010; Available from: http://www.nice.org.uk/guidance/TA190. [Accessed October 2017].
47. National Institute for Health and Care Excellence (NICE). Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer [TA192]. 2010; Available from: http://www.nice.org.uk/guidance/ta192. [Accessed October 2017].
48. National Institute for Health and Care Excellence (NICE). Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer [TA258]. 2012; Available from: http://www.nice.org.uk/guidance/ta258. Last accessed: October 2017.
49. National Institute for Health and Care Excellence (NICE). Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer [TA310]. 2014; Available from: https://www.nice.org.uk/guidance/ta310. [Accessed October 2017].
50. National Institute for Health and Care Excellence (NICE). Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer [TA347]. 2015; Available from: https://www.nice.org.uk/guidance/ta347. [Accessed October 2017].
51. National Institute for Health and Care Excellence (NICE). Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer [TA395]. 2016; Available from: https://www.nice.org.uk/guidance/ta395. [Accessed October 2017].
52. National Institute for Health and Care Excellence (NICE). Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer [TA416]. 2016; Available from: https://www.nice.org.uk/guidance/ta416. [Accessed October 2017].
53. National Institute for Health and Care Excellence (NICE). Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer [TA402]. 2016; Available from: https://www.nice.org.uk/guidance/ta402. [Accessed October 2017].
54. National Institute for Health and Care Excellence (NICE). Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428]. 2017; Available from: https://www.nice.org.uk/guidance/ta428. [Accessed October 2017].
55. National Institute for Health and Care Excellence (NICE). Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA447]. 2017; Available from: https://www.nice.org.uk/guidance/ta447. [Accessed October 2017].
56. European Medicines Agency (EMA). Xalkori: European Public Assessment Report (EPAR). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002489/WC500134759.pdf [Accessed October 2017].
57. Bubendorf L, Buttner R, Al-Dayel F, Dietel M, Elmberger G, Kerr K, *et al.* Testing for ROS1 in non-small cell lung cancer: a review with recommendations. Virchows Archiv : an international journal of pathology. 2016; 469:489-503.
58. U.S. Food and Drug Administration (FDA). FDA approves crizotinib capsules. 2016; Available from:

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm490391.htm [Accessed October 2017].
59. National Institute for Health and Care Excellence (NICE). Crizotinib for treating ROS1-positive advanced non-small cell lung cancer : final scope [ID1098]. 2017; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10127/documents [Accessed October 2017].
60. National Institute for Health and Care Excellence (NICE). Crizotinib in previously treated anaplastic lymphoma kinase NSCLC: Committee papers. Available from: https://www.nice.org.uk/guidance/ta422/documents/committee-papers [Accessed 2017].
61. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998; 52: 377-84.
62. University of York NHS Centre for Reviews and Dissemination (CRD). Systematic reviews: CRD's guidance for undertaking reviews in healthcare. Available from: www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf. [Accessed October 2017].
63. Moro-Sibilot D, Faivre L, Zalcman G, Perol M, Barlesi F, Otto J, *et al.* Crizotinib in patients with advanced ROS1-rearranged non-small cell lung cancer (NSCLC). Preliminary results of the ACSe phase II trial. J Clin Oncol Conference. 2015; 33.
64. Michels S, Gardizi M, Schmalz P, Thurat M, Pereira E, Sebastian M, *et al.* EUCROSS: a European phase II trial of crizotinib in advanced adenocarcinoma of the lung harboring ROS1 rearrangements - preliminary results. J Thorac Oncol 2016; 12:S192.
65. Landi L, Chiari R, Delmonte A, Morabito A, Tamberi S, Barbieri F, *et al.* A07 Crizotinib in ROS1 rearranged or MET deregulated non-small-cell lung cancer (NSCLC): preliminary results of the METROS trial. Annals of oncology : official journal of the European Society for Medical Oncology. 2016; 27:iv5.
66. Goto J, Chih-Hsin Yang J, Kim D, Lu S, Seto R, Yang J, *et al.* Phase II study of crizotinib in east Asian patients (pts) with ROSI-positive advanced non-small cell lung cancer (NSCLC). J Clin Oncol Conference. 2016; 34.
67. Bennati C, Chiari R, Marcomigni L, Minotti V, Giulio M, Scafati C, *et al.* ROS1 rearrangement in lung adenocarcinoma: A retrospective cohort study. Annals of Oncology Conference: 17th National Congress of Medical Oncology Rome Italy Conference Start. 2015; 26.
68. Lu S, Li Z. Differential crizotinib efficacy among ROS1 fusion partners in ROS1-positive non-small cell lung cancer. J Clin Oncol. 2017; 35(Suppl.):Abstr 9067.
69. Zhang L, Jiang T, Zhao C, Li W, Li X, Zhao S, *et al.* Efficacy of crizotinib and pemetrexed-based chemotherapy in Chinese NSCLC patients with ROS1 rearrangement. Oncotarget. 2016.
70. Chen YF, Hsieh MS, Wu SG, Chang YL, Yu CJ, Yang JC, *et al.* Efficacy of pemetrexed-based chemotherapy in patients with ROS1 fusion-positive lung adenocarcinoma compared with in patients harboring other driver mutations in East Asian populations. J Thorac Oncol. 2016; 11:1140-52.
71. Drilon A, Bergagnini I, Delasos L, Sabari J, Woo KM, Plodkowski A, *et al.* Clinical outcomes with pemetrexed-based systemic therapies in RET-rearranged lung cancers. Annals of oncology : official journal of the European Society for Medical Oncology. 2016; 27:1286-91.
72. Liang Y, Wakelee HA, Neal JW. Relationship of driver oncogenes to long-term pemetrexed response in non-small-cell lung cancer. Clinical lung cancer. 2015; 16:366-73.
73. Song Z, Su H, Zhang Y. Patients with ROS1 rearrangement-positive non-small-cell lung cancer benefit from pemetrexed-based chemotherapy. Cancer medicine. 2016; 5:2688-93.
74. Oz B, Batur S, Eralp Y, Hasturk S, Yumuk F, Yildiz O, *et al.* Clinicopathological data's of advanced NSCLC patients with ROS1 gene rearrangement and of clinical responses to crizotinib in Turkey. J Thorac Oncol. 2015; 2:S695.

75. Cook C, Sheets C. Clinical equipoise and personal equipoise: two necessary ingredients for reducing bias in manual therapy trials. J Man Manip Ther. 2011; 19:55-7.
76. Davis KL, Kaye JA, Iyer S. Response rate and outcomes in crizotinib treated advanced ALK-positive NSCLC patients. 16th World Conference on Lung Cancer; September 6-9, 2015; Denver, CO, United States 2015.
77. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. . London2013; Available from: https://www.nice.org.uk/process/pmg9/chapter/1-foreword. Accessed 11 August 2016.
78. Blumenthal GM, Karuri SW, Zhang H, Zhang L, Khozin S, Kazandjian D*, et al.* Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non–small-cell lung cancer: US food and drug administration trial-level and patient-level analyses. J Clin Oncol. 2015; 33:1008-14.
79. EuroQol Group. EQ-5D-3L instrument. 2015; Available from: https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/ [Accessed October 2017].
80. European Organisation for Research and Treatment of Cancer (EORTC). EORTC QLQ-C30. 2016; Available from: http://groups.eortc.be/qol/eortc-qlq-c30 [Accessed October 2017].
81. European Organisation for Research and Treatment of Cancer (EORTC). QLQ-LC13. 2016; Available from: http://groups.eortc.be/qol/sites/default/files/img/specimen_lc13_english.pdf [Accessed October 2017].
82. Kim M, Ahn P, Yang X, Liu T, De Pas L, Crinò S*, et al.* Updated results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). ESMO Congress (2012): Abstract 1230PD. 2012.
83. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB*, et al.* Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. 2012; 13: 1011-9.
84. European Medicines Agency (EMA). Xalkori: EPAR - public assessment report. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002489/WC500134761.pdf. [Accessed October 2017].
85. European Medicines Agency (EMA). Xalkori-H-C-2489-II-0024 : EPAR - assessment report - variation. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002489/WC500200132.pdf. [Accessed October 2017].
86. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health and quality of life outcomes. 2008; 6:84.
87. Blackhall F, Kim DW, Besse B, Nokihara H, Han JY, Wilner KD*, et al.* Patient-reported outcomes and quality of life in PROFILE 1007: a randomized trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer. J Thorac Oncol. 2014; 9:1625-33.
88. Monthly Index of Medical Specialities (MIMS). 2016. Available from: http://www.mims.co.uk/ Accessed: 19th June 2017. .
89. Department of Health. Commercial Medicines Unit. Electronic market information tool (eMit). Available from: http://cmu.dh.gov.uk/electronic-market-information-tool-emit/ [Accessed October 2017].
90. Curtis L BA. Unit costs of health and social care 2015. 2015; Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php?file=full [Accessed October 2017].
91. Department of Health. National Health Service (NHS) national schedule of reference costs 2014-15. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015 [Accessed October 2017].

92. Curtis L, Burns A. Unit costs of health and social care 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php?file=full [Accessed October 2017].
93. Georghiou T BM. Exploring the cost of care at the end of life. 2014; Available from: https://www.nuffieldtrust.org.uk/files/2017-01/end-of-life-care-web-final.pdf [Accessed October 2017].
94. Viola P, Maurya M, Croud J, Gazdova J, Suleman N, Lim E, *et al.* A validation study for the use of ROS1 immunohistochemical staining in screening for ROS1 translocations in lung cancer. J Thorac Oncol. 2016; 11:1029-39.
95. Pfizer confidential contract with NHS for IHC ALK testing.
96. NHS Wales All Wales Genetics Laboratory. Non-small cell lung cancer (NSCLC) – EGFR & ALK mutation testing. Available from: http://www.wales.nhs.uk/sites3/Documents/525/MI-MGN-EGFRInfo.pdf [Accessed October 2017].
97. Digital NHS. Hospital admitted patient care activity, 2015-16: diagnosis. 2016; Available from: http://digital.nhs.uk/catalogue/PUB22378 [Accessed October 2017].
98. National Institute for Health and Care Excellence (NICE). Venous thromboembolic diseases: diagnosis, management and thrombophilia testing [CG144]. 2012; Available from: https://www.nice.org.uk/guidance/CG144 [Accessed 18 October 2017].
99. National Institute for Health and Care Excellence (NICE). TA422: Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (2016). Available at: https://www.nice.org.uk/guidance/ta422. Last accessed: 14th March 2017.

10 APPENDICES

10.1 Analysis populations of the included study and trials

Table 47 Analysis populations of the included study and trials

PROFILE 1001	PROFILE 1014	PROFILE 1007
Response analysis (ORR, DR, TTR, DCR): RE population (n=53) – all patients in the SA population who had an adequate baseline disease assessment Patients also needed to meet one of the two following criteria: 1. Had at least one post-baseline disease assessment at least six weeks from first dose of crizotinib or 2. Withdrew from the study or experienced progressive disease/death at any time on study *Safety analysis (PFS, TTP, TTF, OS, AEs, patient characteristics):* SA population (n=53) – included all enrolled patients who received at least one dose of crizotinib	*Primary analysis (and secondary efficacy analyses):* ITT population (n=343) – included all patients who were randomised to study treatment at the initial randomisation *Safety analyses:* AT population (n=340) – included all patients who received at least one dose of study treatment assigned to them at the initial randomisation *Analysis of PROs:* PRO evaluable population - included all patients from the ITT population who had also completed a baseline PRO assessment and at least one postbaseline PRO	[redacted]

AT=as treated; DCR=disease control rate; DR=duration of response; ITT=intention-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; RE=response evaluable; SA=safety analysis; TTF=time to treatment failure; TTP=time to progression; TTR=time to tumour response
Source: CS, Table 12; TA406 CS, Table 18; CS Appendix L Table 76

10.2 Primary outcomes of the included study and trials

Table 48 Primary outcomes of the included study and trials: definitions, assessment measures and statistical analysis methodology

	PROFILE 1001	PROFILE 1014	PROFILE 1007
Primary outcome	ORR, defined as the percentage of patients with confirmed CR or PR according to RECIST (v1.0 for ROS1+ cohort [n=50]; v1.1 for ALK- cohort [n=3])	PFS, defined as the time from randomisation to RECIST (v1.1)-defined progression (as assessed by IRR) or death	PFS, defined as the time from randomisation to RECIST (v1.0)-defined progression (as assessed by IRR) or to death
Assessment measures	Tumour assessments were performed every 8 weeks in the ROS1+ cohort, and every 6 weeks in the ALK- cohort until RECIST-defined disease progression. Once a patient had completed 15 cycles, tumour assessments reduced to every 16 weeks in the ROS1+ cohort or every 12 weeks in the ALK- cohort, until after 24 cycles in the ROS1+ cohort or 35 cycles in the ALK- cohort. After 24 cycles, tumour assessment was performed every 24 weeks	Tumour assessments were performed every 6 weeks during treatment and at post-treatment follow-up visits (again, scheduled for every 6 weeks) until RECIST-defined progression, as assessed by IRR	Disease assessments were performed at 6-week intervals, i.e. every other cycle, beginning on Day 1 of Cycle 3
Statistical analysis	The point estimate of ORR was provided alongside corresponding 2-sided 95% CIs using the exact method based on the F-distribution	PFS was analysed using the K-M method. 2-sided log-rank tests stratified according to baseline stratification factors were used for between-group comparisons of PFS, with stratified Cox regression models applied to estimate HRs	PFS was summarised using the K-M method and displayed graphically. The median event time for each treatment arm and corresponding 2-sided 95% CI for the median was provided for PFS. A stratified 1-sided log-rank test was used to compare PFS between the two treatment arms. A Cox regression model, stratified for baseline stratification factors, was fitted. The estimated HR and 2-sided 95% CI were provided

ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; HR=hazard ratio; IRR=independent radiology review; K-M=Kaplan-Meier; ORR=objective response rate; PFS=progression-free survival; PR=partial response; RECIST=response evaluation criteria in solid tumours
Source: CS, Table 8, Table 10 and Table 13; TA406 CS, Table 15 and Table 19; CS Appendix L; PROFILE 1007 protocol

10.3 Assessment of proportional hazards

The ERG has assessed the validity of the OS and PFS PH assumptions for the PROFILE 1014 and PROFILE 1007 trials by plotting the cumulative hazard associated with crizotinib treatment versus the cumulative hazard associated with chemotherapy treatment (H-H plot) for each outcome, together with the constant PH trend line. If the PH assumption is valid for these data, the data points should lie close to the trend line and be evenly distributed either side of it. The trend line should also pass through the origin of the graph.

10.3.1 PROFILE 1014

The H-H plot for PFS data from the PROFILE 1014 trial is provided in Figure 19. The data deviate from the linear trend line, and the estimated constant for a linear relationship is statistically significantly different from zero (0.093, 95% CI: 0.077 to 0.109). The graph suggests that the assumption of PH does not hold for PFS data from the PROFILE 1014 trial.

PFS

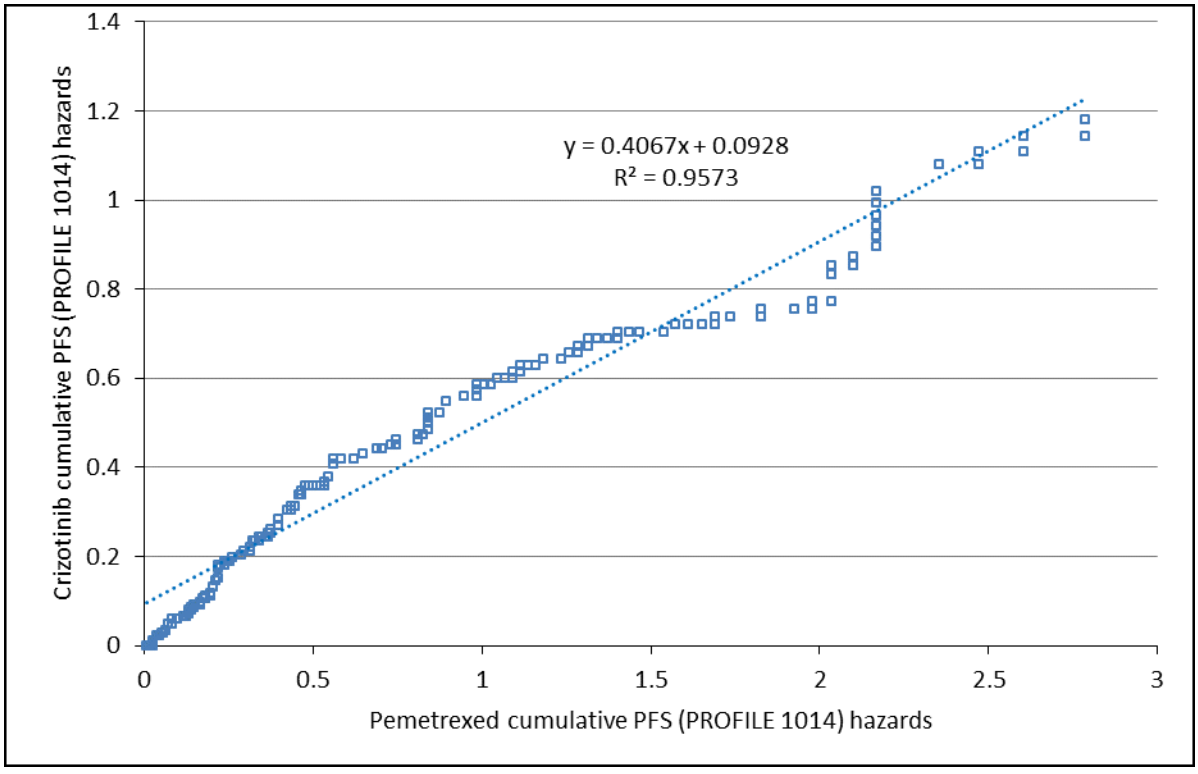


Figure 19 H-H plot for the PROFILE 1014 trial PFS data

PFS=progression-free survival

Unadjusted OS

The H-H plot for unadjusted OS data from the PROFILE 1014 trial is provided in Figure 20. Generally, the data points are reasonably distributed about the trend line. The ERG notes that the estimated constant for a linear relationship is statistically significantly different from zero (-0.016, 95% CI: -0.024 to -0.009), but considers that this may be due to features of the data in the earliest stages of follow-up. Consequently, the ERG is of the opinion that the PH assumption may hold for unadjusted OS data from the PROFILE 1014 trial.

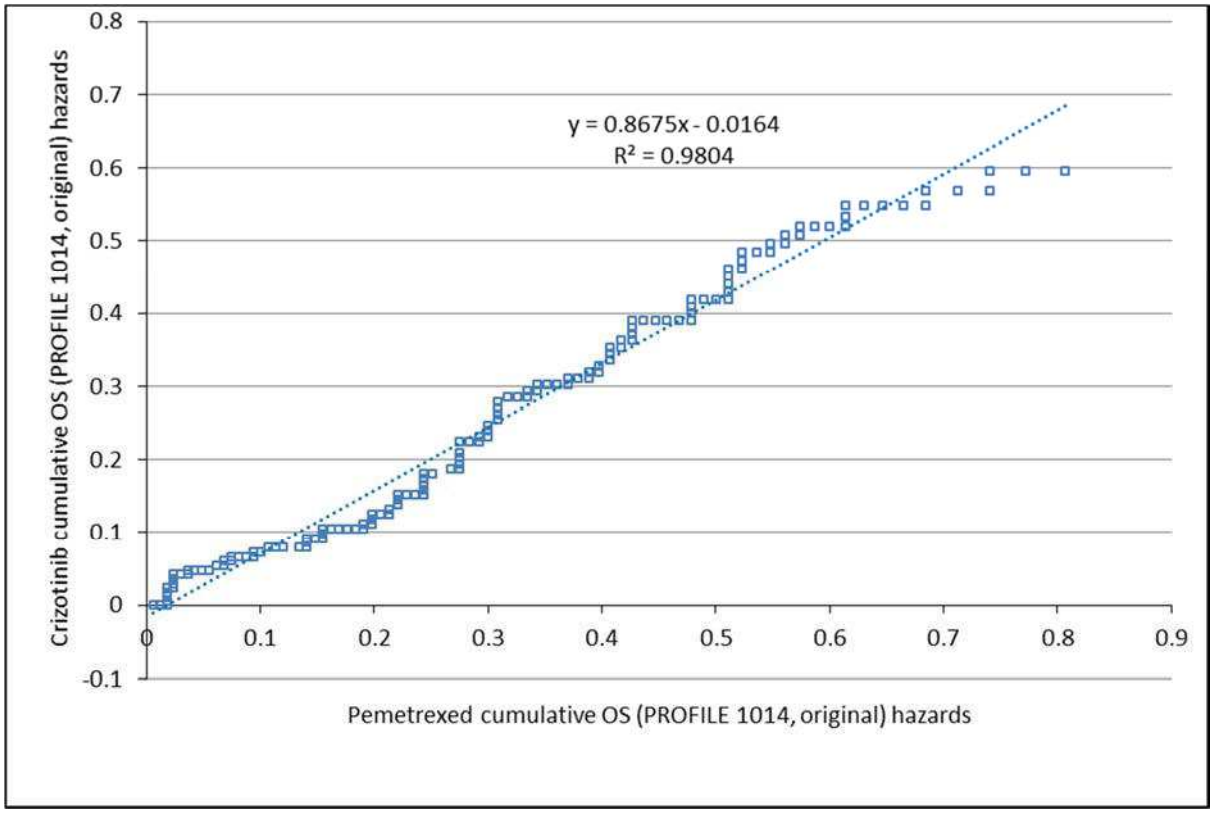


Figure 20 H-H plot for the PROFILE 1014 trial unadjusted OS data

OS=overall survival

RPSFT-adjusted (log-rank test) OS

The H-H plot for RPSFT-adjusted (log-rank test) OS data from the PROFILE 1014 trial is provided in Figure 21. Apart from some systematic deviation in the earliest stages of follow up, the data are reasonably well distributed about the trend line. The ERG notes that the estimated constant for a linear relationship is statistically significantly different from zero (0.017, 95% CI: 0.015 to 0.019), but considers that this may be due to early features of the data. The ERG concludes that the PH assumption may hold for RPSFT-adjusted (log-rank test) OS data from the PROFILE 1014 trial.

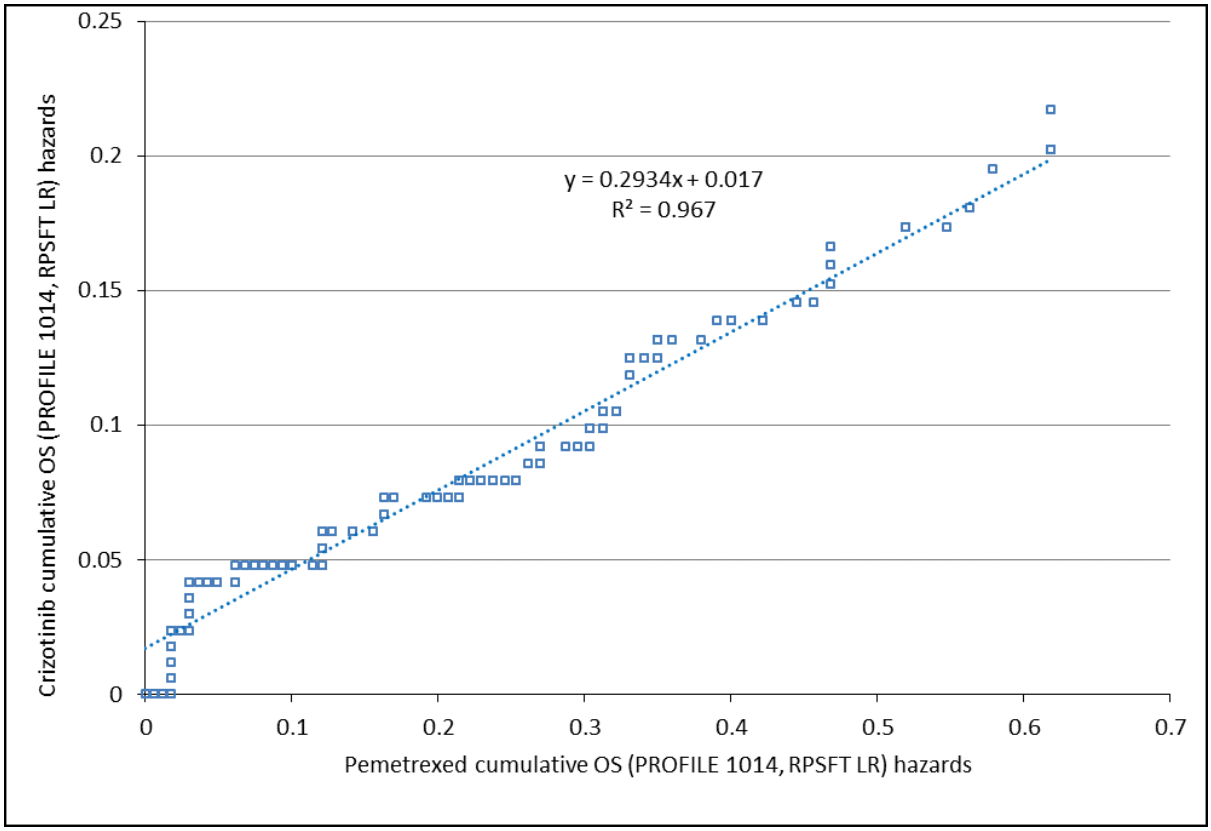


Figure 21 H-H plot for the PROFILE 1014 trial RPSFT-adjusted (log-rank test) OS data

LR=log-rank; OS=overall survival; RPSFT=rank-preserving structural failure time

RPSFT-adjusted (Wilcoxon test) OS

The H-H plot for RPSFT-adjusted (Wilcoxon test) OS data from the PROFILE 1014 trial is provided in Figure 21. Apart from some systematic deviation in the earliest stages of follow up, the data are reasonably well distributed about the trend line. The ERG notes that the estimated constant for a linear relationship is statistically significantly different from zero (0.011, 95% CI: 0.005 to 0.015), but considers that this may be due to early features of the data, and that the PH assumption may hold for RPSFTM-adjusted (Wilcoxon test) OS data from the PROFILE 1014 trial.

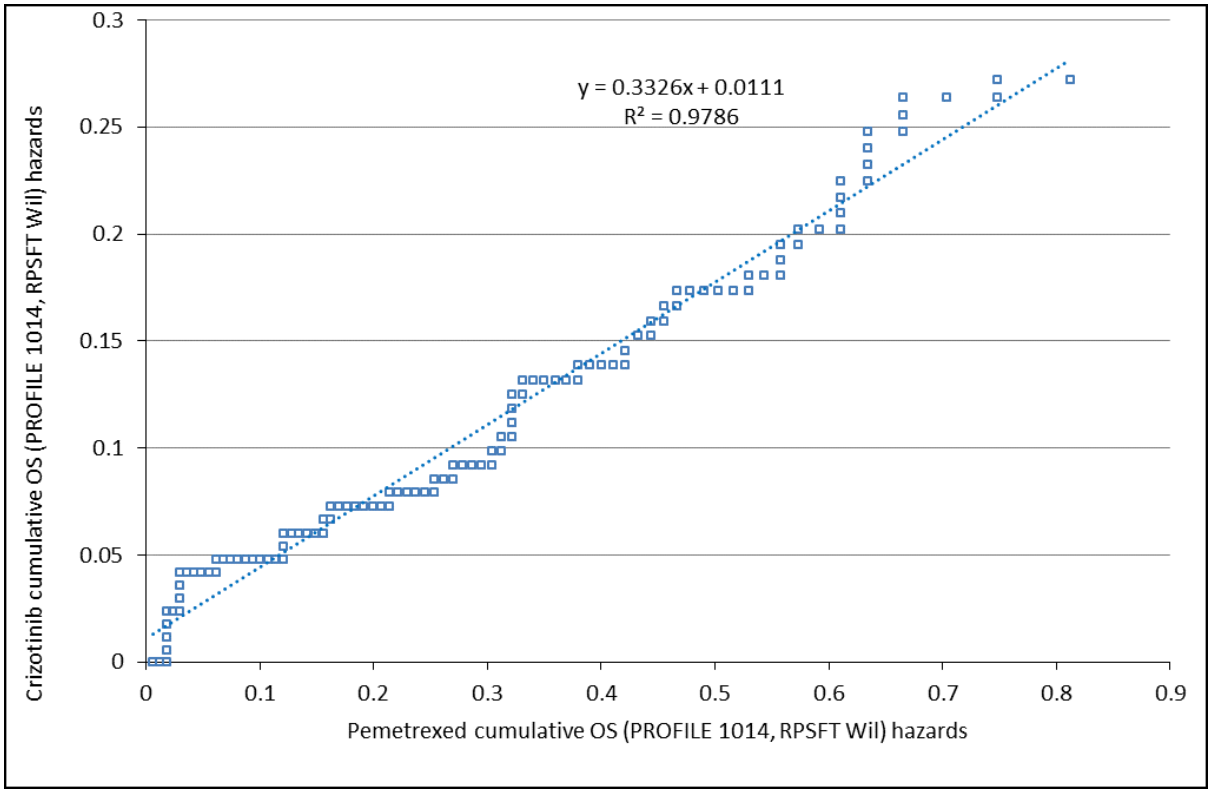


Figure 22 H-H plot for the PROFILE 1014 trial RPSFTM-adjusted (Wilcoxon test) OS data

OS=overall survival; RPSFT=rank-preserving structural failure time model

10.3.2 PROFILE 1007

PFS

The H-H plot for PFS data from the PROFILE 1007 trial is provided in Figure 23. The data deviate from the linear trend line, and the estimated constant for a linear relationship is statistically significantly different from zero (-0.114, 95% CI: -0.133 to -0.094). The graph suggests that the assumption of PH does not hold for PFS data from the PROFILE 1007 trial.

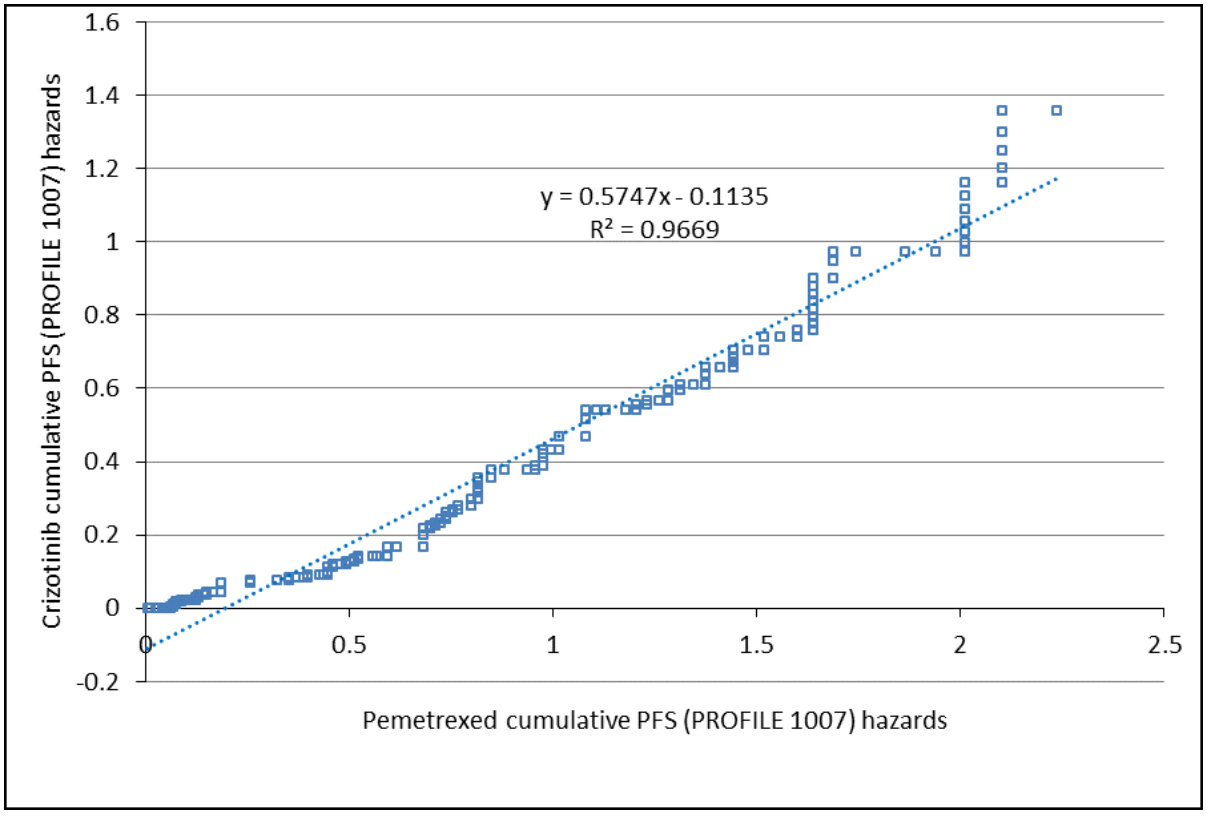
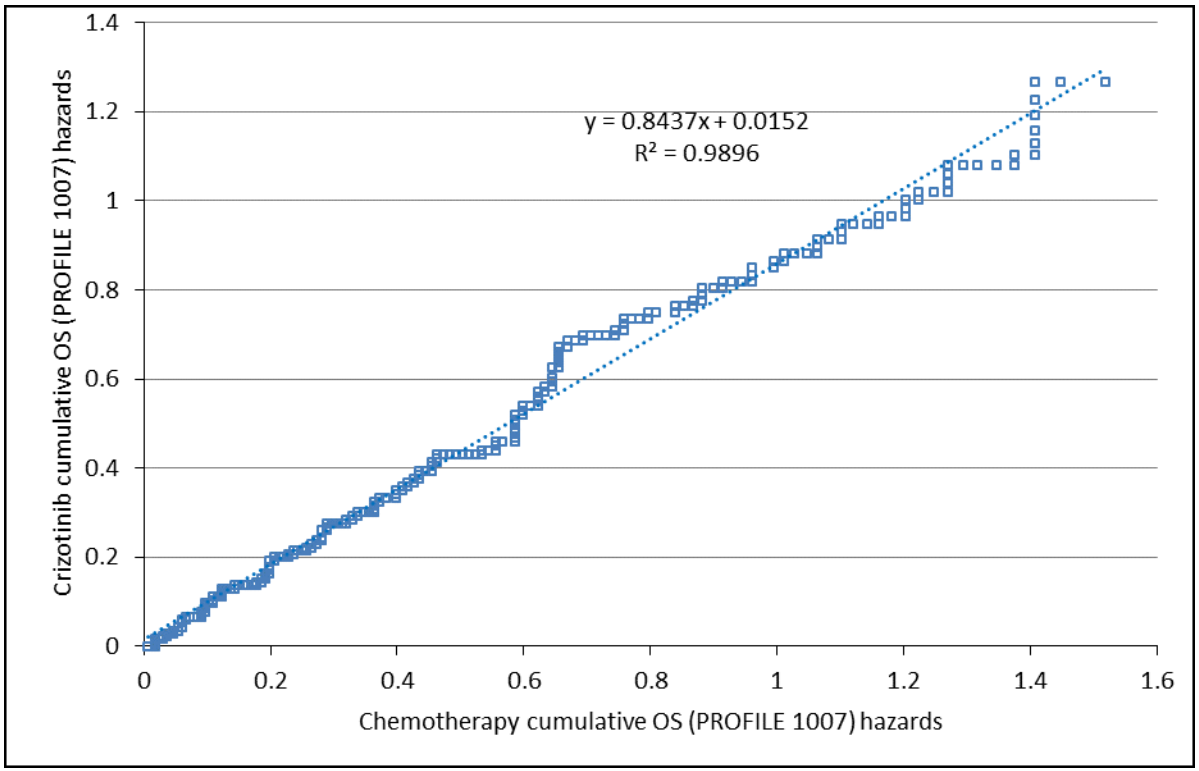


Figure 23 H-H plot for the PROFILE 1007 trial PFS data

PFS=progression-free survival

Unadjusted OS

The H-H plot for OS data from the PROFILE 1007 trial is provided in Figure 23. The data are reasonably well distributed about the trend line. The ERG notes that the estimated constant for a linear relationship is statistically significantly different from zero (0.015, 95% CI: 0.008 to 0.023), but generally there is not strong evidence to suggest that the PH assumption is violated. The ERG considers that the assumption of PH may hold for unadjusted OS data from the PROFILE 1007 trial.



OS=overall survival

10.4 ERG assessment of statistical approach used to analyse data from the included study and trials

Table 49 ERG assessment of statistical approach used to analyse data from the included study and trials

	PROFILE 1001	PROFILE 1014	PROFILE 1007
Sample size calculation	The sample size calculation is presented in Table 13 of the CS. The ERG is satisfied that this sample size calculation was pre-specified in the supplemental TSAP (p7-8).	The sample size calculation is presented in Table 19 of the TA406 CS. The ERG is satisfied that this sample size calculation was pre-specified in the TSAP (p9).	The sample size calculation is presented in Table 75 of Appendix L of the CS. The ERG is satisfied that this sample size calculation was pre-specified in the TSAP (p8).
Protocol amendments	Protocol amendments were listed in the final protocol (p2-5). All protocol amendments were made before the time of data cut-off (30th November 2014), and so were unlikely to have been driven by the results of the trial.	Protocol amendments were listed in the final protocol (p2-5). All but the last two of the protocol amendments were made before the time of data cut-off [redacted], and so were unlikely to have been driven by the results of the trial. The final protocol amendment specified post-hoc analyses to evaluate treatment activity in patients with or without brain metastases, and post-hoc analyses of PFS, ORR, OS and AEs by type of chemotherapy. The ERG is satisfied that the methods of analysis presented in the amended TSAP were appropriate.	Protocol amendments were listed in the final protocol (p2-5). All protocol amendments were made before the time of data cut-off (31st August 2015), and so were unlikely to have been driven by the results of the trial.
Subgroup analyses	Subgroup analyses were pre-specified for ORR according to baseline characteristics in the TSAP (p23). Results of subgroup analyses are presented in Appendix E of the CS.	Subgroup analyses were pre-specified for PFS, ORR, and OS according to baseline characteristics in the TSAP (p17). Results of subgroup analyses are presented in the CSR (p147, p383-400, p639).	Pre-planned subgroup analyses for PFS, ORR, and OS are available in the TSAP (p15). Results of subgroup analyses are presented in the preliminary CSR for PFS (p90) and the final CSR for OS (p110). The results of subgroup analyses for ORR have not been made available to the ERG.

	PROFILE 1001	PROFILE 1014	PROFILE 1007
Sensitivity analyses	Although the primary analysis of ORR was based on derived tumour assessment (investigator assessment), IRR was also carried out in the ROS1+ cohort (n=50). IRR was not performed for tumour scans from the three ALK- NSCLC patients who were retrospectively found to be ROS1+ due to differences in RECIST versions used and treatment cycle lengths. The ERG is satisfied that the additional efficacy analysis based on IRR were pre-planned in the supplemental TSAP (p19-20). A summary of the results of this additional efficacy analysis is available in the CS (p58), but full results have not been made available to the ERG.	Pre-planned sensitivity analyses of the primary endpoint are available in the TSAP (p21-22). Results of sensitivity analyses for PFS are presented in the CSR (p148).	Pre-planned sensitivity analyses of the primary endpoint are available in the TSAP (p19). Results of sensitivity analyses for PFS are presented in the preliminary CSR (pp90-91).
Safety analysis	Included the type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory parameters. AEs were classified and graded according to the CTCAE v3.0. In accordance with the plan for analysis of AEs outlined in the supplemental TSAP (pp18-19), many different summaries of AEs are provided as summary tables and as narrative descriptions in the CSR (Section 12).	Included the type, incidence, severity, timing, seriousness, and relatedness of AEs and laboratory parameters. AEs were classified and graded according to the CTCAE v4.0. In accordance with the plan for analysis of AEs outlined in the TSAP (pp26-32), many different summaries of AEs are provided as summary tables and as narrative descriptions in the CSR (Section 12).	Included the type, incidence, severity, seriousness and relationship to study medications of AEs and any laboratory abnormalities. AEs were classified and graded according to the CTCAE v4.0. In accordance with the plan for analysis of AEs outlined in the TSAP (pp23-28), many different summaries of AEs are provided as summary tables and as narrative descriptions in the CSR (Section 12).

	PROFILE 1001	PROFILE 1014	PROFILE 1007
Analysis of PROs	N/A	PROs were assessed using the EORTC QLQ-C30, the lung cancer specific module (QLQ-LC13), the EQ-5D questionnaire, and the VSAQ-ALK. Patients completed the self-administered EORTC QLQ-C30, QLQ-LC13, VSAQ-ALK, and EQ-5D questionnaires on Day 1 of each cycle until EOT/withdrawal, and prior to any testing, treatment, or discussion with the physician or site personnel. The EORTC QLQ-C30 and QLQ-LC13 were also to be administered on Day 7 and Day 15 of Cycle 1. Detailed statistical methodology of PROs is presented in the TSAP (pp32-34). The ERG is satisfied that the methodology used to analyse PROs was appropriate, and that all results are reported in the CSR (pp163-179).	PROs were assessed using the EORTC QLQ-C30, the lung cancer specific module (QLQ-LC13), the EQ-5D questionnaire, and the VSAQ-ALK. Patients completed the self-administered questionnaires at baseline, Day 1 of every cycle, at the EOT or withdrawal, and prior to any testing, treatment, or discussion with the physician or clinic personnel. Detailed statistical methodology of PROs is presented in the TSAP (pp28-31). The ERG is satisfied that the methodology used to analyse PROs was appropriate, and that all results are reported in the preliminary CSR (pp106-118) and the final CSR (pp114-117).

AEs=adverse events; ALK=anaplastic lymphoma kinase; CS=company submission; CSR=clinical study report; CTCAE=common terminology criteria for adverse events; EORTC=European Organisation for Research on the Treatment of Cancer; ERG=evidence review group; EOT=end of treatment; EQ-5D=EuroQol-5D; IRR=independent radiology review; N/A=not applicable; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcome; QLQ-LC13=EORTC lung cancer-specific quality of life questionnaire; QLQ-C30=Quality of Life Questionnaire-Core 30; RECIST=Response Evaluation Criteria on Solid Tumours; TSAP=trial statistical analysis plan; VSAQ-ALK=Visual Symptom Assessment Questionnaire-ALK

Source: CS, Table 9, Table 13; TA406 CS, Table 17; CS Appendix L, Table 75; PROFILE 1001 CSR; PROFILE 1014 CSR; PROFILE 1007 CSR; ERG comment

10.5 ERG PROFILE 1001 time-to-event modelling

The ERG's investigated projecting time-to-event data based on using the K-M data directly from the PROFILE 1001 study and appending a parametric projection based on the trend identified in the latter part of the dataset. This method assumes that time-to-event data are sufficiently mature to have settled into a long term trend and that this trend can be identified in the data. The data in the PROFILE 1001 study are immature and based on a small sample (n=53), so the results of the ERG's remodelling should be treated with caution.

Given the paucity of data in the PROFILE 1001 study, an exponential curve was fitted to minimise parameter assumptions. The face validity of the exponential fit can be assessed by cumulative hazard plots (Figure 24, Figure 25, Figure 26), since an exponential cumulative hazard results in a straight line when plotted against time. The exponential curve has good face validity for OS and TTD, but is a less good fit for PFS.

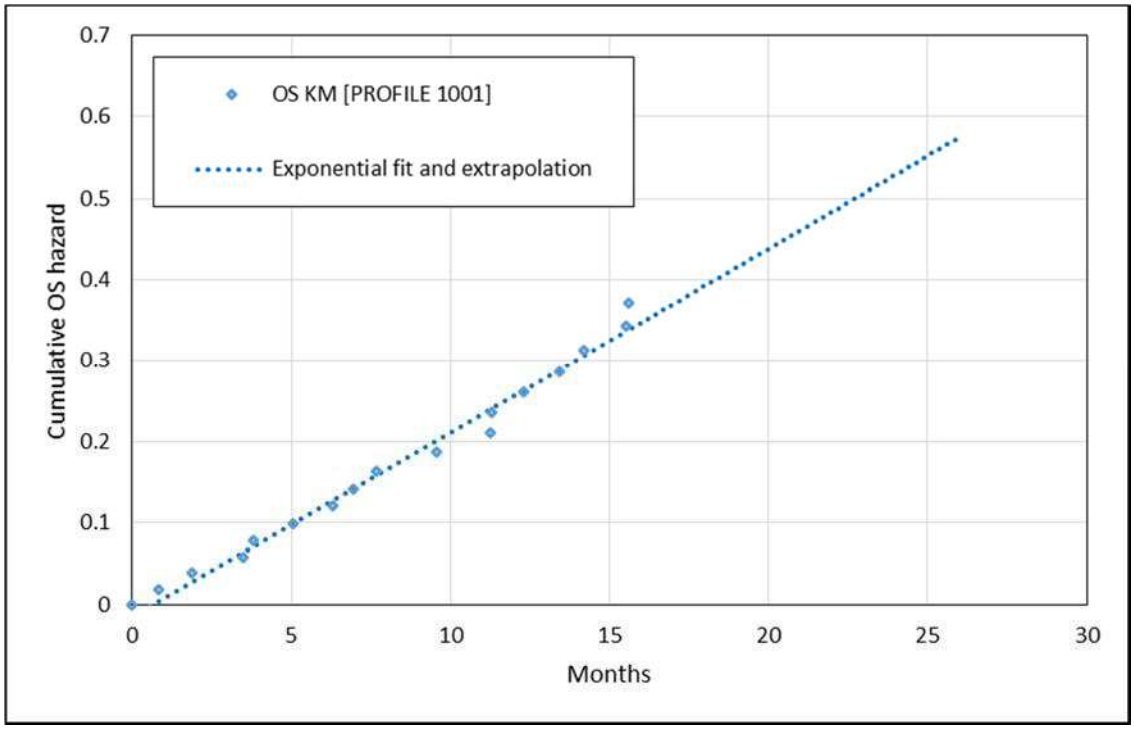


Figure 24 Cumulative OS hazard and ERG fitted exponential model: PROFILE 1001

KM=Kaplan-Meier; OS=overall survival

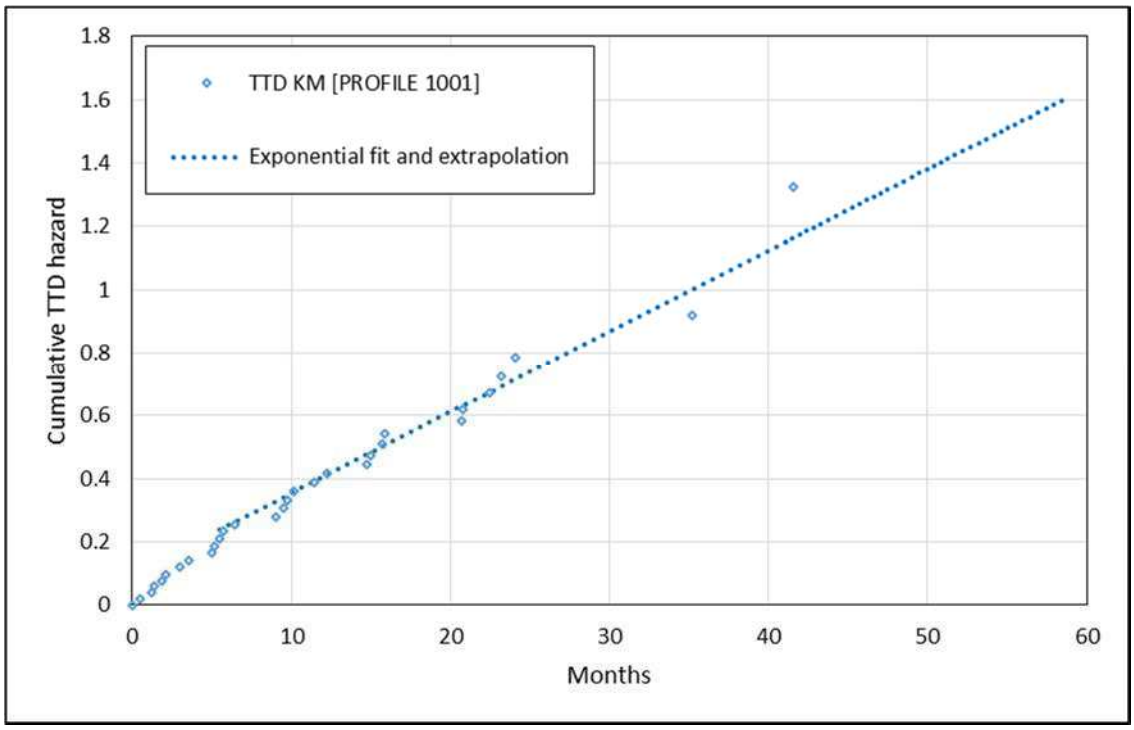


Figure 25 Cumulative TTD hazard and ERG fitted exponential model: PROFILE 1001

KM=Kaplan-Meier; TTD=time-to-treatment discontinuation

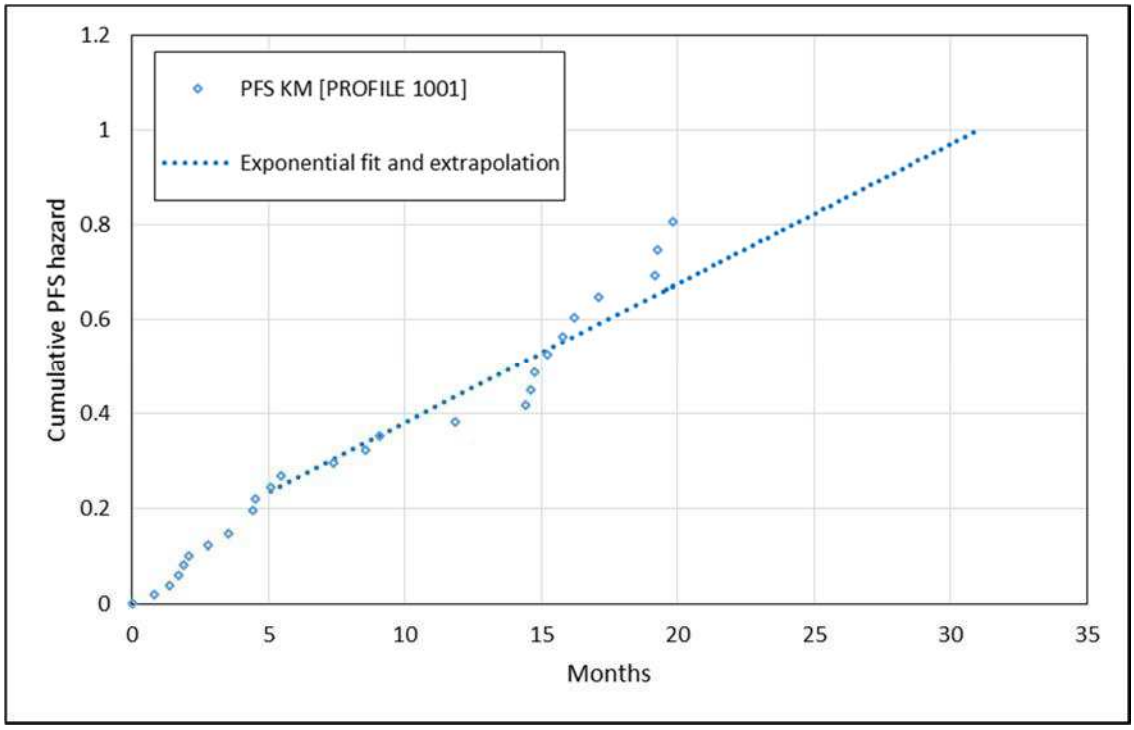


Figure 26 Cumulative PFS hazard and ERG fitted exponential model: PROFILE 1001

KM=Kaplan-Meier; PFS=progression free survival

10.6 ERG Revisions to company's model

All revisions are activated by a logic switch. Logic switches are indicated by named range variables Mod_*number* where *number* = 1 to 8. A menu of revisions and Mod names appears below and on the 'Base case results' worksheet in the ERG amended model.

Instructions for modifying the updated company model (received 1 November 2017)

1. Populate the following named switch values in the 'Base case results' sheet

Name	Switch	Details	Switch options					
			1		2		3	
			Revision #	*Revision*	*Revision #*	*Revision*	*Revision #*	*Revision*
Mod_1	0	ERG first line OS [PROFILE 1014]	R1a)	PFS HR	R1b)	PPS=PPS		
Mod_2	0	ERG first-line OS treatment effect [PROFILE 1001]	R2a)	PFS HR	R2b)	PPS=PPS		
Mod_3	0	ERG first-line remodel crizotinib [PROFILE 1001]	R3)	KM+exponential				
Mod_4	0	ERG subsequent-line OS [PROFILE 1007]	R4a)	PFS HR (applied to ERG crizotinib)	R4b)	PPS=PPS (applied to ERG crizotinib)		
Mod_5	0	ERG subsequent-line OS treatment effect [PROFILE 1001]	R5	PPS=PPS				
Mod_6	0	ERG subsequent-line remodel crizotinib [PROFILE 1001]	R6)	KM+exponential				
Mod_7	0	ERG first line PFS utility	R7a)	0.81	R7b)	0.72	R7c)	Pemetrexed = 0.75
Mod_8	0	ERG subsequent-line PFS utility	R8a)	-0.03 crizotinib	R8b)	+0.03 docetaxel		

2. Move all sheets from *ID1098_ ERG additional model data.xlsx* into the model

3. For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'Modified formulae' column in the table below

- paste formulae into the cells referred to in the ‘Cells’ column in the table below

For individual revisions:

R1, R4, R7 and R8: Please set the model to base case (in Model controls! sheet)

R1: Please set the PROFILE 1014 crossover adjustment to “Unadjusted” (Model controls! J118)

R2, R3, R5 and R6: Please set the model to PROFILE 1001 scenario (in Model controls! sheet)

For scenarios/combined revisions:

If scenario contains R1 or R4: Please set the model to base case (in Model controls! sheet)

If scenario contains R1: Please set the PROFILE 1014 crossover adjustment to “Unadjusted” (Model controls! J118)

If scenario contains R2, R3, R5 or R6: Please set the model to PROFILE 1001 scenario (in Model controls! sheet)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R1 ERG first line OS [1014] R2 ERG first-line OS treatment effect [1001] R3 ERG first-line remodel crizotinib [1001]	Mod_1 Mod_2 Mod_3	OS (1L)	Q88:Q2358	Pemetrexed+platinum =IF(con_survival_ALK="No",OFFSET(Q87,1,VLOOKUP(con_OS_model_pem,Lists_parametric_models,2,FALSE),),IF(con_updated_1014_data="No",X88,Y88))*IF(AND(Mod_1=0,Mod_2=0,Mod_3=0),1,0)+'ERG first-line'!E11*IF(AND(Mod_1=1,Mod_2=0,Mod_3=0),1,0)+'ERG first-line'!F11*IF(AND(Mod_1=2,Mod_2=0,Mod_3=0),1,0)+'ERG first-line'!H11*IF(AND(Mod_1=0,Mod_2=1,Mod_3=0),1,0)+'ERG first-line'!I11*IF(AND(Mod_1=0,Mod_2=2,Mod_3=0),1,0)+'ERG first-line'!K11*IF(AND(Mod_1=0,Mod_2=0,Mod_3=1),1,0)
R3 ERG first-line remodel crizotinib [1001]	Mod_3	OS (1L)	E88:E2358	Crizotinib =IF(con_survival_ALK="No",OFFSET(E87,1,VLOOKUP(con_OS_model_criz,Lists_parametric_models,2,FALSE),),IF(con_updated_1014_data="No",L88,M88))*IF(Mod_3=0,1,0)+'ERG first-line'!J11*IF(Mod_3=1,1,0)
R3 ERG first-line remodel crizotinib [1001]	Mod_3	PFS (1L)	E85:E2355	Crizotinib =IF(con_survival_ALK="No",OFFSET(E84,1,VLOOKUP(con_PFS_model_criz,Lists_parametric_models,2,FALSE),),L85)*IF(Mod_3=0,1,0)+'ERG first-line'!L11*IF(Mod_3=1,1,0)
R3 ERG first-line remodel crizotinib [1001]	Mod_3	PFS (1L)	Q85:Q2355	Pemetrexed+platinum =IF(con_survival_ALK="No",OFFSET(Q84,1,VLOOKUP(con_PFS_model_pem,Lists_parametric_models,2,FALSE),),X85)*IF(Mod_3=0,1,0)+'ERG first-line'!M11*IF(Mod_3=1,1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R3 ERG first-line remodel crizotinib [1001]	Mod_3	TOT (1L)	E60:E2330	Crizotinib =IF(con_survival_ALK="No",OFFSET(E59,1,VLOOKUP(con_TTF_model_criz,Lists_parametric_models,2,FALSE),),L60)*IF(Mod_3=0,1,0)+'ERG first-line'!N11*IF(Mod_3=1,1,0)
R4 ERG subsequent-line OS [1007] R6 ERG subsequent-line remodel crizotinib [1001]	Mod_4 Mod_6	OS (subsequent-line)	E90:E2360	Crizotinib =IF(con_survival_ALK="No",OFFSET(E89,1,VLOOKUP(con_OS_model_criz,Lists_parametric_models,2,FALSE),),L90)*IF(AND(Mod_4=0,Mod_6=0),1,0)+'ERG subsequent-line'!D11*IF(AND(OR(Mod_4=1,Mod_4=2),Mod_6=0),1,0)+'ERG subsequent-line'!J11*IF(AND(Mod_4=0,Mod_6=1),1,0)
R4 ERG subsequent-line OS [1007] R5 ERG subsequent-line OS treatment effect [1001] R6 ERG subsequent-line remodel crizotinib [1001]	Mod_4 Mod_5 Mod_6	OS (subsequent-line)	P90:P2360	Docetaxel =IF(con_survival_ALK="No",OFFSET(P89,1,VLOOKUP(con_OS_model_doc,Lists_parametric_models,2,FALSE),),W90)*IF(AND(Mod_4=0,Mod_5=0,Mod_6=0),1,0)+'ERG subsequent-line'!E11*IF(AND(Mod_4=1,Mod_5=0,Mod_6=0),1,)+'ERG subsequent-line'!F11*IF(AND(Mod_4=2,Mod_5=0,Mod_6=0),1,0)+'ERG subsequent-line'!I11*IF(AND(Mod_4=0,Mod_5=1,Mod_6=0),1,0)+'ERG subsequent-line'!K11*IF(AND(Mod_4=0,Mod_5=0,Mod_6=1),1,0)
R6 ERG subsequent-line remodel crizotinib [1001]	Mod_6	PFS (subsequent-line)	E87:E2357	Crizotinib =IF(con_survival_ALK="No",OFFSET(E86,1,VLOOKUP(con_PFS_model_criz,Lists_parametric_models,2,FALSE),),L87)*IF(Mod_6=0,1,0)+'ERG subsequent-line'!L11*IF(Mod_6=1,1,0)
R6 ERG subsequent-line remodel crizotinib [1001]	Mod_6	PFS (subsequent-line)	P87:P2357	Docetaxel =IF(con_survival_ALK="No",OFFSET(P86,1,VLOOKUP(con_PFS_model_doc,Lists_parametric_models,2,FALSE),),W87)*IF(Mod_6=0,1,0)+'ERG subsequent-line'!M11*IF(Mod_6=1,1,0)

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R6 ERG subsequent-line remodel crizotinib [1001]	Mod_6	TOT (subsequent-line)	E60:E2330	Crizotinib =IF(con_survival_ALK="No",OFFSET(E59,1,VLOOKUP(con_TTF_model_criz,Lists_parametric_models,2,FALSE),),L60)*IF(Mod_6=0,1,0)+'ERG subsequent-line'!N11*IF(Mod_6=1,1,0)
R7 ERG first line PFS utility	Mod_7	Utilities	C33	Crizotinib =VLOOKUP(D33,$D$13:$E$14,2,FALSE)*IF(Mod_7<>2,1,0)+C15*IF(Mod_7=2,1,0)
R7 ERG first line PFS utility	Mod_7	Utilities	C34	Pemetrexed+platinum =VLOOKUP(D34,$D$15:$E$15,2,FALSE) *IF(AND(Mod_7<>1,Mod_7<>3),1,0)+C13*IF(Mod_7=1,1,0)+0.75*IF(Mod_7=3,1,0)
R8 ERG subsequent-line PFS utility	Mod_8	Utilities	C38	Crizotinib =VLOOKUP(D38,$D$23:$E$24,2,FALSE)*IF(Mod_8<>1,1,0)+(C23-0.03)*IF(Mod_8=1,1,0)
R8 ERG subsequent-line PFS utility	Mod_8	Utilities	C39	Docetaxel =VLOOKUP(D39,$D$25:$E$25,2,FALSE)*IF(Mod_8<2,1,0)+(C25+0.03)*IF(Mod_8=2,1,0)